

YOUR ESSENTIAL GUIDE TO THE MANAGEMENT
OF THE ACUTELY ILL PATIENT

OXFORD HANDBOOK OF ACUTE MEDICINE

Punit S. Ramrakha | Kevin P. Moore | Amir Sam



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Oxford Handbook of Acute Medicine

FOURTH EDITION

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OXFORD
UNIVERSITY PRESS

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Great Clarendon Street, Oxford, OX2 6DP,
United Kingdom

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
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First edition published 1997

Second edition published 2004

Third edition published 2010

Fourth edition published 2019

Impression: 1

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Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America

British Library Cataloguing in Publication Data

Data available

Library of Congress Control Number: 2018941855

ISBN 978-0-19-879742-5

Printed and bound in China by
C&C Offset Printing Co., Ltd.

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Foreword to fourth edition

The first edition of the *Oxford Handbook of Acute Medicine* was published in 1997. Since then, acute medicine has evolved as a fully established specialty within the UK, and over 95% of hospitals now have an acute medical unit. Importantly, acute medicine is developing in Europe and Australia as part of providing high-quality care for patients presenting as a medical emergency to hospital. Such patients now constitute the largest group of patients occupying inpatient hospital beds. It is imperative therefore that all staff are trained in the management of acute medical emergencies and, importantly, have easy access to information to support the management of this acutely unwell subgroup of patients. This textbook is clearly structured and is supported by useful diagrams and algorithms, and hence the information is readily accessible. The practical procedure section is comprehensive. While many practising clinicians will not be required to undertake all these procedures, they will be involved in discussion on these issues with patients and relatives, and this text will be an invaluable guide.

The handbook series from Oxford University Press already provides useful information to many clinicians working in clinical practice. Irrespective of age or seniority, for clinicians directly involved in the early diagnosis and management of patients who present acutely, this book will provide a concise aid. The clear and up-to-date content of this text reflects the experience of the authors, and I am personally delighted to provide a foreword to a book which will undoubtedly help support the growing number of trainees working in the field of acute medicine.

Derek Bell
Professor of Acute Medicine
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Preface

The management of acute medical emergencies is the most demanding and rewarding aspect of medical training. The aim of this handbook is to give confidence to junior doctors to manage acute medical problems effectively and safely. This edition has been updated to ensure that every aspect of the care recommended is in line with current clinical guidelines. The fourth edition of the *Oxford Handbook of Acute Medicine* includes summary boxes for the key points in the management of common medical emergencies. These concise and practical 'management key points' can be a useful guide to junior doctors in the emergency department. The layout of the book reflects clinical practice: assessment, differential diagnosis, immediate management, and some aspects of long-term therapy. Throughout the book, the text commonly exceeds that required for the management of specialist problems by the generalist. This is deliberate, but intended, to provide the doctor with an understanding of specialist interventions, so that they are more conversant with what is possible and what is happening to their patient. We have included a new section on acute medicine and the older patient.

A word of advice—patients who present acutely ill are frequently scared and need to be kept informed and to feel safe, however busy you are. Being admitted to hospital means you lose control of your life. Thus, it is our duty as their doctor to make all of our patients feel safe and cared for, and to keep them informed of plans and what is happening to them.

Acknowledgements

We would like to thank all of the contributors who provided initial drafts of chapters which have evolved over time, as well as friends and colleagues who gave up their time to read a chapter and verify its accuracy. We would also like to thank OUP for their encouragement during the re-writing of this book. PSR is indebted to Sanjana, Aarav, and Dhruv for their support and motivation. KPM is indebted to Janet, Alice, and Thomas for their continued patience when the portable computer accompanied family holidays. Finally, we would like to acknowledge the environment at the Hammersmith Hospital where we trained and learned that acute medicine is both interesting and fun.

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Symbols and abbreviations

↗	cross reference
↑	increased
↓	decreased
→	leading to
~	approximately
🌐	website
α	alpha
β	beta
δ	delta
♀	female
♂	male
>	greater than
<	less than
≥	equal to or greater than
≤	equal to or less than
±	plus or minus
°C	degree Celsius
®	registered trademark
™	trademark
©	copyright
A&E	accident and emergency
AA	Alcoholics Anonymous
AAA	abdominal aortic aneurysm
AAV	ANCA-associated vasculitis
Ab	antibody
ABG	arterial blood gas
ABPI	ankle–brachial pressure index
ACEI	angiotensin-converting enzyme inhibitor
ACE-III	Addenbrooke's Cognitive Examination-III
AChR	acetylcholine receptor
ACS	acute coronary syndrome
ACT	artemisinin-based combination therapy; activated clotting time
ACTH	adrenocorticotrophic hormone
AD	adrenaline
ADH	antidiuretic hormone
AF	atrial fibrillation
AFB	acid-fast bacilli

Ag	antigen
AGEP	acute generalized exanthematous pustulosis
AIDS	acquired immunodeficiency syndrome
AKI	acute kidney injury
ALI	acute lung injury
ALL	acute lymphoblastic leukaemia
ALP	alkaline phosphatase
ALS	advanced life support
ALT	alanine transaminase
AMA	anti-mitochondrial antibody
AMHP	approved mental health professional
AML	acute myeloid leukaemia
AMU	acute medical unit
ANA	anti-nuclear antibody
ANCA	anti-neutrophil cytoplasmic antibody
AP	anteroposterior
APL	acute promyelocytic leukaemia
APSAC	anisoylated plasminogen streptokinase activator complex (anistreplase)
APTT	activated partial thromboplastin time
AR	aortic regurgitation
ARB	angiotensin receptor blocker
ARDS	adult respiratory distress syndrome
ARF	acute renal failure
ASA	acetyl salicylic acid
ASD	atrial septal defect
ASPECTS	Alberta Stroke Programme Early CT score
AST	aspartate transaminase
ATN	acute tubular necrosis
ATP	adenosine triphosphate
AV	atrioventricular
AVF	arteriovenous fistula
AVNRT	atrioventricular-nodal re-entry tachycardia
AVPU	Alert, Voice, Pain, Unresponsive
AVR	aortic valve replacement
AVRT	accessory pathway tachycardia
AXR	abdominal X-ray
BAL	bronchoalveolar lavage
BBV	bloodborne virus
bd	twice a day
BIH	benign intracranial hypertension

BiPAP	bilevel positive airway pressure
BJ	Bence-Jones
BLS	basic life support
BMT	bone marrow transplant
BNF	<i>British National Formulary</i>
BOOP	bronchiolitis obliterans organizing pneumonia
BP	blood pressure
bpm	beat per minute
BTS	British Thoracic Society
Ca ²⁺	calcium
CABG	coronary artery bypass graft
CAD	coronary artery disease
CAH	congenital adrenal hyperplasia
cal	calorie
CAM	confusion assessment method
cAMP	cyclic adenosine monophosphate
CAP	community-acquired pneumonia
CAVH	continuous arteriovenous haemofiltration
CAVHD	continuous arteriovenous haemodiafiltration
CBD	common bile duct
CCDC	Consultant in Communicable Disease Control
CCF	congestive cardiac failure
CCHF	Congo–Crimean haemorrhagic fever
CCl ₄	carbon tetrachloride
CCP	cyclic citrullinated peptide
CCU	coronary care unit
CEA	carcinoembryonic antigen
CGA	comprehensive geriatric assessment
CHB	complete heart block
CIN	contrast nephropathy
CIWA-Ar	Clinical Institute Withdrawal Assessment of Alcohol
CK	creatine kinase
CK-MB	creatine kinase-muscle/brain
cmH ₂ O	centimetre of water
CMR	cardiac magnetic resonance
CMV	cytomegalovirus; continuous mandatory ventilation
CNI	calcineurin inhibitor
CNS	central nervous system
CO	cardiac output; carbon monoxide
CO ₂	carbon dioxide
COHb	carboxy-haemoglobin

COP	cryptogenic organizing pneumonia
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airways pressure
CPK	creatinine phosphokinase
CPR	cardiopulmonary resuscitation
CrAg	cryptococcal antigen
CRF	chronic renal failure
CRP	C-reactive protein
CSF	cerebrospinal fluid
CSM	carotid sinus massage
CT	computed tomography
CTPA	CT pulmonary angiography
CVA	cerebrovascular accident
CVP	central venous pressure
CVH	continuous venovenous haemofiltration
CVHD	continuous venovenous haemodiafiltration
CXR	chest X-ray
2D	two-dimensional
D&V	diarrhoea and vomiting
DA	dopamine
DAA	direct acting antiviral
DAPT	dual antiplatelet therapy
DAT	direct antigen test
DBP	diastolic blood pressure
DC	direct current
DDAVP	desmopressin
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DKA	diabetic ketoacidosis
dL	decilitre
DM	diabetes mellitus
DMARD	disease-modifying anti-rheumatic drug
DMSA	dimercaptosuccinic acid
DNA	deoxyribonucleic acid
DNACPR	do not attempt cardiopulmonary resuscitation
DRESS	drug reaction with eosinophilia and systemic symptoms
dsDNA	double-stranded deoxyribonucleic acid
DSH	deliberate self-harm
DSN	diabetes specialist nurse
DT	delerium tremens
DU	duodenal ulcer

DVLA	Driver and Vehicle Licensing Authority
DVT	deep vein thrombosis
DXA	dual-energy X-ray absorptiometry
EBV	Epstein–Barr virus
ECG	electrocardiogram
Echo	echocardiogram
ECT	ecarin clotting time; electroconvulsive therapy
ECV	extracellular volume
EDTA	ethylenediaminetetraacetic acid
EEG	electroencephalogram
EF	ejection fraction
EGPA	eosinophilic granulomatosis with polyangiitis
ELISPOT	enzyme-linked immunospot
EM	electron microscopy; erythema multiforme
EMD	electromechanical dissociation
EMG	electromyogram
ENA	extractable nuclear antigen
ENT	ear, nose, and throat
EPS	electrophysiological studies
ERCP	endoscopic retrograde cholangiopancreatography
ESR	erythrocyte sedimentation rate
ET	endotracheal
ETT	endotracheal tube
EUS	endoscopic ultrasound scan
F	French
FAB	French-American-British (classification)
FBC	full blood count
FDG-PET	fludeoxyglucose positron emission tomography
FDP	fibrinogen degradation product
Fe ²⁺	ferrous
Fe ³⁺	ferric
Fe ⁴⁺	ferryl
FEIBA	factor VIII inhibitor bypassing activity
FEV ₁	forced expiratory volume in 1 second
FFP	fresh frozen plasma
FGF	fibroblast growth factor
FiO ₂	fraction of inspired oxygen
fL	femtolitre
FLAIR	fluid attenuation inversion recovery
FNAB	fine-needle aspiration biopsy
FRC	functional residual capacity

FSGS	focal segmental glomerulosclerosis
FSH	follicle-stimulating hormone
FVC	forced vital capacity
g	gram
G	gauge
G6PD	glucose-6-phosphate dehydrogenase
G&S	group and save
GABA	gamma-aminobutyric acid
GAHs	Glasgow Alcoholic Hepatitis Score
GB	gall bladder
GBL	gamma-butyrolactone
GBM	glomerular basement membrane
GBS	Guillain–Barré syndrome
GCS	Glasgow Coma Scale
GCSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GH	growth hormone
GHB	gamma-hydroxybutyric acid
GI	gastrointestinal
GIT	gastrointestinal tract
GP	glycoprotein; general practitioner
GPA	granulomatosis with polyangiitis
GTN	glyceryl trinitrate
GUM	genitourinary medicine
GVHD	graft-versus-host disease
h	hour
HAART	highly active antiretroviral therapy
HACEK	Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella spp.
HAV	hepatitis A virus
Hb	haemoglobin
HBc	hepatitis B core
HB _e	hepatitis B envelope
HB _e Ag	hepatitis B envelope antigen
HBIG	hepatitis B immunoglobulin
HB _s	hepatitis B surface
HB _s Ab	hepatitis B surface antibody
HB _s Ag	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma

HCG	human chorionic gonadotrophin
HCN	hydrogen cyanide
Hct	haematocrit
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDU	high dependency unit
HELLP	haemolysis, elevated liver enzyme levels, and low platelet levels
HEV	hepatitis E virus
HFRS	haemorrhagic fever with renal syndrome
HGV	heavy goods vehicle
HHS	hyperosmolar hyperglycaemic syndrome
HIAA	hydroxyindole acetic acid
Hib	<i>Haemophilus influenzae</i> b
HIDA	hepatobiliary iminodiacetic acid
HITT	heparin-induced thrombocytopenia and thrombosis
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
HMG-CoA	hydroxymethyl glutaryl-coenzyme A
HMMA	hydroxymethylmandelic acid
HOCM	hypertrophic obstructive cardiomyopathy
HONK	hyperosmolar non-ketotic coma
HPS	hantavirus pulmonary syndrome
HR	heart rate
HRCT	high-resolution computed tomography
HRS	hepatorenal syndrome
HRT	hormone replacement therapy
HSV	herpes simplex virus
HTLV	human T-lymphotropic virus
HUS	haemolytic uraemic syndrome
I:E	inspiratory:expiratory ratio
IABP	intra-aortic balloon pump
IBD	inflammatory bowel disease
ICD	implantable cardioverter defibrillator
ICP	intracranial pressure
ICU	intensive care unit
ID	infectious diseases
IE	infective endocarditis
Ig	immunoglobulin
IgA	immunoglobulin A
IgE	immunoglobulin E

IgG	immunoglobulin G
IgM	immunoglobulin M
IGF	insulin growth factor
IHD	ischaemic heart disease
IIH	idiopathic intracranial hypertension
IJV	internal jugular vein
IL	interleukin
IM	intramuscular
in	inch
INR	international normalized ratio
IPPV	intermittent positive pressure ventilation
IRIS	immune reconstitution inflammatory syndrome
ITP	idiopathic thrombocytopenic purpura
ITU	intensive therapy unit
IU	international unit
IV	intravenous
IVC	inferior vena cava
IVDU	intravenous drug user
IVI	intravenous infusion
IVIG	intravenous immunoglobulin
IVU	intravenous urogram
J	joule
JVP	jugular venous pressure
K ⁺	potassium
KCl	potassium chloride
KDIGO	Kidney Disease Improving Global Outcomes
kg	kilogram
kPa	kilopascal
KS	Kaposi's sarcoma
KUB	kidneys, ureters, and bladder
L	litre
LA	left atrium
LAD	left anterior descending coronary artery
LBBS	left bundle branch block
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
LGV	lymphogranuloma venereum
LH	luteinizing hormone
LHRH	luteinizing hormone-releasing hormone
LIJ	left internal jugular

LK-1	liver kidney-1
LMA	laryngeal mask airway
LMN	lower motor neuron
LMS	left main stem
LMWH	low-molecular-weight heparin
LP	lumbar puncture
LRTI	lower respiratory tract infection
LSD	lysergic acid diethylamide
LV	left ventricular
LVAD	left ventricular assist device
LVEDP	left ventricular end diastolic pressure
LVF	left ventricular failure
LVH	left ventricular hypertrophy
m	metre
MACE	major adverse cardiac events
MAHA	microangiopathic haemolytic anaemia
MAI	<i>Mycobacterium avium intracellulare</i>
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure
MAT	multifocal atrial tachycardia
MC&S	microscopy, culture, and sensitivity
MCA	middle cerebral artery
MCD	minimal change disease
MCH	mean cell haemoglobin
MCTD	mixed connective tissue disease
MCV	mean corpuscular volume
MDMA	'ecstasy' / 3,4-methylenedioxymethamphetamine
MDR	multidrug-resistant
MDS	myelodysplastic syndrome
MEN	multiple endocrine neoplasia
mEq	milliequivalent
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
METS	metabolic equivalents
mg	milligram
Mg ²⁺	magnesium
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	myocardial infarction
MIBG	meta-iodobenzylguanidine
micromol	micromole
min	minute

mL	millilitre
mm	millimetre
mmHg	millimetre of mercury
mmol	millimole
MMSE	Mini Mental State Examination
MoCA	Montreal cognitive assessment
MOF	multi-organ failure
mOsm	milliosmole
MPGN	membranoproliferative glomerulonephritis
MR	magnetic resonance; mitral regurgitation
MRA	magnetic resonance angiography
MRCP	magnetic resonance cholangio-pancreatography
MRI	magnetic resonance imaging
MRSA	meticillin-resistant <i>Staphylococcus aureus</i>
ms	millisecond
MS	multiple sclerosis
MSM	men who have sex with men
MSSA	meticillin-sensitive <i>Staphylococcus aureus</i>
MSU	midstream urine
mU	milliunit
MUGA	multigated acquisition (scan)
mV	millivolt
MV	mitral valve
MVP	mitral valve prolapse
MVR	mitral valve replacement
MVT	monomorphic ventricular tachycardia
Na ⁺	sodium
NA	noradrenaline
NABQI	<i>N</i> -acetyl- <i>p</i> -benzoquinoneimine
nAnB	non-A/non-B (hepatitis)
NaTHNaC	National Travel Health Network and Centre
NBM	nil by mouth
NBTV	non-bacterial thrombotic vegetation
NCS	nerve conduction studies
ng	nanogram
NG	nasogastric
NHL	non-Hodgkin's lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHSS	National Institutes of Health Stroke Scale
NIPPV	nasal intermittent positive pressure ventilation

NIV	non-invasive ventilation
NJ	nasojejunal
NMB	neuromuscular blockade
nmol	nanomole
NMS	neuroleptic malignant syndrome
NOAC	new oral anticoagulant
NPIS	National Poisons Information Service
NPS	novel psychoactive substance
NPV	negative pressure ventilation
NQ-MI	non-Q-wave MI
nsAH	non-sedating antihistamine
NSAID	non-steroidal anti-inflammatory drug
NSTE-ACS	non-ST-elevation acute coronary syndrome
NSTEMI	non-ST elevation myocardial infarction
NYHA	New York Heart Association
O ₂	oxygen
OCP	oral contraceptive pill
od	once a day
OD	overdose
OGD	oesophagogastroduodenoscopy
OPG	orthopentamogram
OSA	obstructive sleep apnoea
OTC	over-the-counter
PA	pulmonary artery
P _a CO ₂	partial pressure of carbon dioxide in arterial blood
PAIR	puncture, aspiration, injection, and re-aspiration
PAN	polyarteritis nodosa
P _a O ₂	partial pressure of oxygen in arterial blood
PAWP	pulmonary artery wedge pressure
PBC	primary biliary cirrhosis
PCA	patient-controlled analgesia
PCC	prothrombin complex concentrate
PCI	percutaneous coronary intervention
PCP	<i>Pneumocystitis jiroveci</i> (<i>carinii</i>) pneumonia
PCR	polymerase chain reaction
PCV	packed cell volume
PCWP	pulmonary capillary wedge pressure
PD	peritoneal dialysis
PDA	patent ductus arteriosus
PDI	phosphodiesterase inhibitor
PE	pulmonary embolism; phenytoin equivalent

PEA	pulseless electrical activity
PEEP	positive end-expiratory pressure
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
PEG	percutaneous endoscopic gastrostomy
PEP	post-exposure prophylaxis
PET	positron emission tomography
PFO	patent foramen ovale
PFT	pulmonary function test
PHI	primary HIV infection
PiCCO	pulse contour cardiac output
PML	progressive multifocal leukoencephalopathy
PMN	polymorphonuclear cells (neutrophils)
pmol	picomole
PMR	polymyalgia rheumatica
PO	<i>per os</i> (by mouth)
PO_4^{3-}	phosphate
PPI	proton pump inhibitor
PR	per rectum
PRES	posterior reversible encephalopathy syndrome
PRN	<i>pro re nata</i> (as required)
PSA	prostate-specific antigen
PSC	primary sclerosing cholangitis
PSP	primary spontaneous pneumothorax
PT	prothrombin time
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related peptide
PTT	partial thromboplastin time
PTU	propylthiouracil
PUO	pyrexia of unknown origin
PVC	polyvinyl chloride
PVE	prosthetic valve endocarditis
PVR	pulmonary vascular resistance
PVT	polymorphic ventricular tachycardia
q	every
qds	four times a day
QwMI	Q-wave myocardial infarction
RA	right atrium/atrial; rheumatoid arthritis
RAD	right axis deviation
RBBB	right bundle branch block
RBC	red blood cell

RCA	right coronary artery
RCP	Royal College of Physicians
RCT	randomized controlled trial
Rh	rhesus (factor)
RhF	rheumatoid factor
RiCof	ristocetin cofactor
RIJ	right internal jugular
RNA	ribonucleic acid
RNP	ribonucleic protein
rPA	recombinant plasminogen activator
RR	respiratory rate
RRT	renal replacement therapy
RSV	respiratory syncytial virus
RTA	road traffic accident
rtPA	recombinant tissue plasminogen activator
RUQ	right upper quadrant
RV	right ventricular
RVEDP	right ventricular end-diastolic pressure
RVF	right ventricular failure
RVOT	right ventricular outflow tract
SADQ	Severity of Alcohol Dependence Questionnaire
SAH	subarachnoid haemorrhage
SARS	severe acute respiratory syndrome
SBE	subacute bacterial endocarditis
SBP	systolic blood pressure; spontaneous bacterial peritonitis
SCAR	severe cutaneous adverse reactions
SCM	sternocleidomastoid
SCV	subclavian vein
SD	standard deviation
SDHB	succinate dehydrogenase subunit B
SDHD	succinate dehydrogenase subunit D
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SIMV	synchronized intermittent mandatory ventilation
SIRS	systemic inflammatory response syndrome
SJS	Stevens–Johnson syndrome
SpO ₂	oxygen saturation in blood
SK	streptokinase
SL	sublingual
SLE	systemic lupus erythematosus
SM	smooth muscle
SNRI	serotonin–noradrenaline reuptake inhibitor

SOL	space-occupying lesion
spp.	species
SR	slow release
SSP	secondary/spontaneous pneumothorax
SSPE	subacute sclerosing panencephalitis
SSRI	selective serotonin reuptake inhibitor
SSSS	staphylococcal scalded skin syndrome
STEMI	ST elevation myocardial infarction
STI	sexually transmitted infection
STS	serological tests for syphilis
SVC	superior vena cava
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
SXR	skull X-ray
T3	tri-iodothyronine
T4	thyroxine
TACO	transfusion-associated circulatory overload
TB	tuberculosis
TBG	thyroxine-binding globulin
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
tds	three times a day
TEN	toxic epidermal necrolysis
TENS	transcutaneous electrical nerve stimulation
TFT	thyroid function test
TIA	transient ischaemic attack
TIBC	total iron binding capacity
TIPS	transvenous intrahepatic portosystemic shunting
TNF	tumour necrosis factor
TnI	troponin I
TnT	troponin T
TOE	transoesophageal echocardiogram
tPA	tissue plasminogen activator
TPMT	thiopurine methyltransferase
TPN	total parenteral nutrition
TPR	temperature, pulse, and respiratory rate
TRALI	transfusion-related acute lung injury
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone
TT	thrombin time
TTE	transthoracic echocardiography

TTP	thrombotic thrombocytopenic purpura
TURP	transurethral resection of the prostate
U&Es	urea and electrolytes
U	unit
UA	unstable angina
UC	ulcerative colitis
UDCA	ursodeoxycholic acid
UFH	unfractionated heparin
UK	United Kingdom
UMN	upper motor neuron
URTI	upper respiratory tract infection
US	ultrasound
USS	ultrasound scan
UTI	urinary tract infection
UV	ultraviolet
V	volt
VALI	ventilator-associated lung injury
VE	ventricular extrasystole
VF	ventricular fibrillation
VHF	viral haemorrhagic fever
VMA	vanillyl mandelic acid
VOR	vestibulo-ocular reflex
VPB	ventricular premature beats
V/Q	ventilation (V)/perfusion (Q)
VRE	vancomycin-resistant enterococci
VSD	ventricular septal defect
VT	ventricular tachycardia
VTE	venous thromboembolism
vWD	von Willebrand's disease
vWF	von Willebrand factor
VZIG	varicella-zoster immune globulin
VZV	varicella-zoster virus
WBC	white blood cell
WCC	white cell count
WE	Wernicke's encephalopathy
WG	Wegener's granulomatosis
WHO	World Health Organization
WPW	Wolff-Parkinson-White
ZN	Ziehl-Neelsen

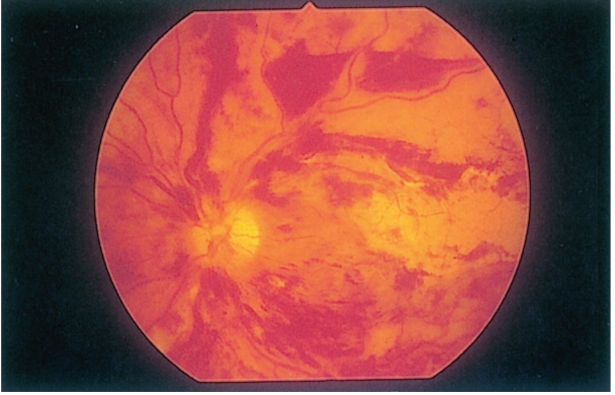


Fig. 6.1 Central retinal vein occlusion with assorted closure of the arterial circulation above the macula. Reproduced from Easty D, et al. *Oxford Textbook of Ophthalmology*, 1999, with permission from Oxford University Press.

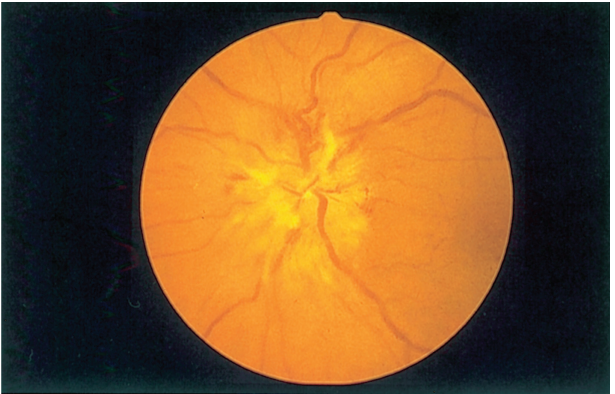


Fig. 6.2 Acute papilloedema. Reproduced from Easty D, et al. *Oxford Textbook of Ophthalmology*, 1999, with permission from Oxford University Press.



Fig. 7.1 Erythema nodosum. The lesions can be very faint, but are indurated and painful on palpation. Reproduced from MacKie R. *Clinical Dermatology*, 2003, with permission from Oxford University Press.

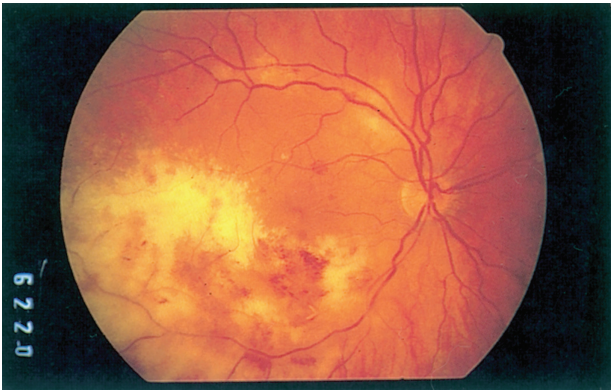


Fig. 8.2 The typical appearance of cytomegalovirus retinitis in a patient with AIDS, characterized by retinal necrosis with an irregular granular border, patchy retinal haemorrhage, and retinal inflammatory sheathing of the retinal vessels. Reproduced from Easty D, et al. *Oxford Textbook of Ophthalmology*, 1999, with permission from Oxford University Press.



Fig. 12.1 Morbilliform eruption caused by administration of ampicillin to a patient with infectious mononucleosis. Reproduced from MacKie R. *Clinical Dermatology*, 2003, with permission from Oxford University Press.



Fig. 12.2 Erythema multiforme on the leg, note the presence of target lesions. Reproduced from MacKie R. *Clinical Dermatology*, 2003, with permission from Oxford University Press.



Fig. 12.3 Blisters of bullous pemphigoid. Large, tense, raised lesions are seen on an erythematous eczematized base. Reproduced from MacKie R. *Clinical Dermatology*, 2003, with permission from Oxford University Press.

Cardiac emergencies

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Adult basic life support

Basic life support is the backbone of effective resuscitation following a cardiorespiratory arrest. The aim is to maintain adequate ventilation and circulation until the underlying cause for the arrest can be reversed. A duration of 3–4min without adequate perfusion (less if the patient is hypoxic) will lead to irreversible cerebral damage. The usual scenario is an unresponsive patient found by staff who alert the cardiac arrest team. The initial assessment described next should have already been performed by the person finding the patient. The same person should have also started cardiopulmonary resuscitation (CPR). Occasionally, you will be the first to discover the patient and it is important to rapidly assess the patient and begin CPR. The various stages in basic life support are described here and summarized in Fig. 1.1.

1. Assessment of the patient

- *Ensure safety of the rescuer and victim.*
- *Check whether the patient is responsive.* Gently shake the victim and ask loudly, 'Are you all right?'
- If the victim responds, place them in the recovery position and get help.
- If the victim is unresponsive, shout for help and move on to assess airway.

2. Airway assessment

- *Open the airway.* With two fingertips under the point of the chin, tilt the head up. If this fails, place your fingers behind the angles of the lower jaw, and apply steady pressure upwards and forwards. Remove ill-fitting dentures and any obvious obstruction. If the patient starts breathing, roll the patient over into the recovery position and try to keep the airway open until an oropharyngeal airway can be inserted (see Fig. 1.2).
- *Keep airway open; look, listen, and feel for breathing.* Look for chest movements; listen at the victim's mouth for breathing sounds, and feel for air on your cheek (for no more than 10s).
 - If the patient is breathing, turn them into the recovery position, check for continued breathing, and get help.
 - If the patient is not breathing or making occasional gasps or weak attempts at breathing, send someone for help. Start rescue breaths by giving two slow, effective breaths, each resulting in a visible rise and fall in the chest wall.

3. Assessment of circulation

- Assess signs of circulation by feeling the carotid pulse for no more than 10s.
 - If there are signs of circulation, but no breathing, continue rescue breaths and check for a circulation every 10 breaths (approximately every minute).
 - If there are no signs of circulation, start chest compression at a rate of 100 times per minute. Combine rescue breaths and compression at a rate of 30 compressions to two effective breaths.
- The ratio of compressions to lung inflation remains the same for resuscitation with two persons.

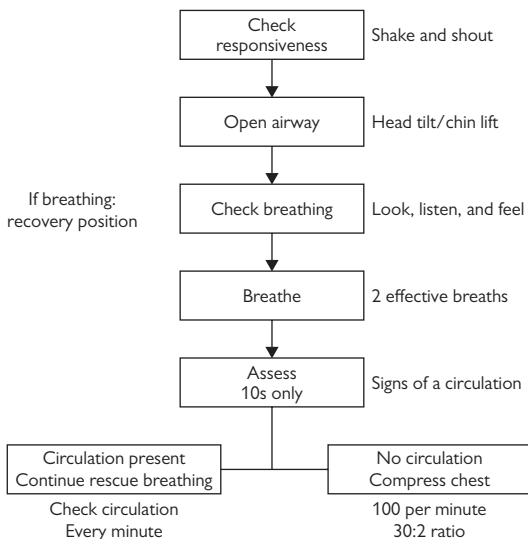


Fig. 1.1 Adult basic life support. Send or go for help as soon as possible, according to guidelines. For further information, see the Resuscitation Council (UK) website <http://www.resus.org.uk>

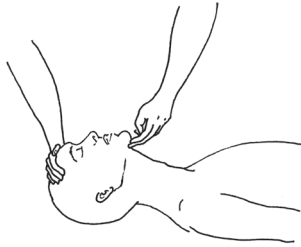
Adult advanced life support

- It is unlikely that an effective spontaneous cardiac activity will be restored by basic life support without more advanced techniques (intubation for effective ventilation, drugs, defibrillation, etc.). Do not waste time. As soon as help arrives, delegate CPR to someone less experienced in advanced life support (ALS), so that you are able to continue.
- Attach the patient to a cardiac monitor as soon as possible to determine the cardiac rhythm, and treat appropriately (➡ Universal treatment algorithm, pp. 8–9).
- Oropharyngeal (Guedel) or nasopharyngeal airways help maintain the patency of the airway by keeping the tongue out of the way (see Fig. 1.2). They can cause vomiting if the patient is not comatose. Endotracheal (ET) intubation is the best method of securing the airway. Do not attempt this if you are inexperienced.
- Establish venous access. Central vein cannulation (internal jugular or subclavian) is ideal but requires more training and practice and is not for the inexperienced. If venous access fails, drugs may be given via an ET tube (ETT) into the lungs (except for bicarbonate and calcium salts). Double the doses of drugs if using this route, as absorption is less efficient than intravenously (IV).

Post-resuscitation care

- *Try to establish the events* that precipitated the arrest from the history, staff, witnesses, and hospital notes of the patient. Is there an obvious cause [myocardial infarction (MI), hypoxia, hypoglycaemia, stroke, drug overdose or interaction, electrolyte abnormality, etc.]? Record the duration of the arrest in the notes, with the interventions and drugs (and doses) in chronological order.
- *Examine the patient* to check both lung fields are being ventilated. Check for ribs that may have broken during CPR. Listen for any cardiac murmurs. Check the neck veins. Examine the abdomen for an aneurysm or signs of peritonism. Insert a urinary catheter. Consider a nasogastric (NG) tube if the patient remains unconscious. Record the Glasgow Coma Scale (GCS) score (➡ Glasgow Coma Scale, p. 458), and perform a brief neurological assessment (➡ Coma: assessment, pp. 348–9).
- *Investigations:* *electrocardiogram (ECG)*—looking for MI, ischaemia, tall T-waves ($\uparrow K^+$); *arterial blood gas (ABG)*—mixed metabolic and respiratory acidosis is common and usually responds to adequate oxygenation and ventilation once the circulation is restored. If severe, consider bicarbonate; *chest X-ray (CXR)*—check position of ETT, look for pneumothorax; *urea and electrolytes (U&Es)*; and *glucose*.
- After early and successful resuscitation from a primary cardiac arrest, the patient may rapidly recover completely. The patient must be transferred to the high dependency unit (HDU) or coronary care unit (CCU) for monitoring for 12–24h. Commonly, the patient is unconscious post-arrest and should be transferred to the intensive therapy unit (ITU) for ventilation and haemodynamic monitoring and support for ≥ 24 h.
- Change any venous lines that were inserted at the time of arrest for central lines inserted with a sterile technique. Insert an arterial line, and consider a pulmonary artery (PA) catheter (Swan–Ganz) if requiring inotropes.

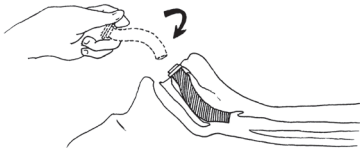
- Remember to talk to the relatives. Keep them informed of events, and give a realistic (if bleak) picture of the arrest and possible outcomes.
- When appropriate, consider the possibility of organ donation and do not be frightened to discuss this with the relatives. Even if discussion with the relatives is delayed, remember corneas and heart valves may be used up to 24h after death (➡ Brain death, p. 468).



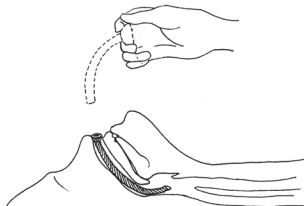
Jaw lift to open the airway



Jaw thrust (thrust the angle of the mandible upwards)



Insertion of oropharyngeal airway [start with the tip pointing cranially (towards the nose) and rotate 180° as you insert, so that it finally points into the larynx as shown]



Insertion of nasopharyngeal airway (follow the curve of the nasal passage to introduce into the larynx)

Fig. 1.2 Insertion of an oropharyngeal and nasopharyngeal airway.

Universal treatment algorithm

- Cardiac rhythms of cardiac arrest can be divided into two groups (see Fig. 1.3):
 - Ventricular fibrillation (VF)/ventricular tachycardia (VT).
 - Non-VF/VT [asystole and pulseless electrical activity (PEA)].
- The principal difference in treatment of the two groups of arrhythmias is the need for attempted defibrillation in the VF/VT group of patients.
- Fig. 1.3 summarizes the algorithm for management of both groups of patients.

VF/VT

VF/VT are the most common rhythms at the time of cardiac arrest. Success in treatment of VF/VT is dependent on *prompt defibrillation*. With each passing minute in VF, the chance of successful defibrillation declines by 7–10%.

- Defibrillation in the current guidelines involves a single shock of 150–200J biphasic (or 360J monophasic). Chest compressions should be continued while the defibrillator is charged.
- Each shock should be immediately followed by CPR, without reassessing the rhythm or feeling for a pulse. This is because if a perfusing rhythm has not been restored, delay in trying to palpate the pulse will further compromise the myocardium. If a perfusing rhythm has been restored, the pulse is rarely palpable immediately after defibrillation, and giving compressions does not enhance the chance of VF recurring. In the event of post-shock asystole, compressions may induce VF.
- Current guidelines suggest a ratio of 30 chest compressions to 2 breaths. When the airway is secured, chest compressions can be continued without pausing during ventilation.
- Continue CPR for 2min, and then pause briefly to check the monitor.
- If VF/VT persists, give a further (2nd shock) of 150–360J biphasic (or 360J monophasic).
- Resume CPR immediately and continue for 2min, then pause briefly to check the monitor.
- If VF/VT persists, give a 3rd shock of 150–360J biphasic (360J monophasic) and resume CPR. Give adrenaline 1mg and amiodarone 300mg once chest compressions have restarted.
- Continue CPR for 2min, then pause briefly to check the monitor.
- Give adrenaline before alternate shocks (approximately every 3–5min): 1mg IV or via intra-osseous route.
- In between cycles of defibrillation, reversible factors must be identified and corrected, the patient intubated (if possible), and venous access obtained. If organized electrical activity is seen (when the monitor is checked at points suggested earlier in this algorithm), check for a pulse.
 - If present: start post-resuscitation care.
 - If pulse absent: switch to the non-VF/VT side of the algorithm.
- *Precordial thump*. This has a low success rate for cardioversion of a shockable rhythm and is only effective if given within the first few seconds of the onset of a shockable rhythm. It must not delay defibrillation. It is therefore only really appropriate in a witnessed, monitored arrest, e.g. on the CCU or in the cardiac catheter laboratory.

Non-VF/VT (asystole and PEA)

- The outcome from these rhythms is generally worse than for VF/VT, unless a reversible cause can be identified and treated promptly.

- Chest compressions and ventilation (30:2) should be undertaken for 2min with each loop of the algorithm. When airway is secured, chest compressions can be continued without pausing during ventilation.
- Recheck the rhythm after 2min. If organized electrical activity is seen, check for a pulse.
 - If present: start post-resuscitation care.
 - If absent: continue CPR.
 - If VF/VT: change to the VF/VT side of the algorithm.
- Give adrenaline 1mg IV as soon as intravascular access is achieved and with alternate loops (every 3–5min).
- In asystole, if P waves are present on the strip/monitor, pacing (external or transvenous) must be considered.
- Identification of the underlying cause (see Fig. 1.3) and its correction are both vital for successful resuscitation. Resuscitation must be continued while reversible causes are being sought.

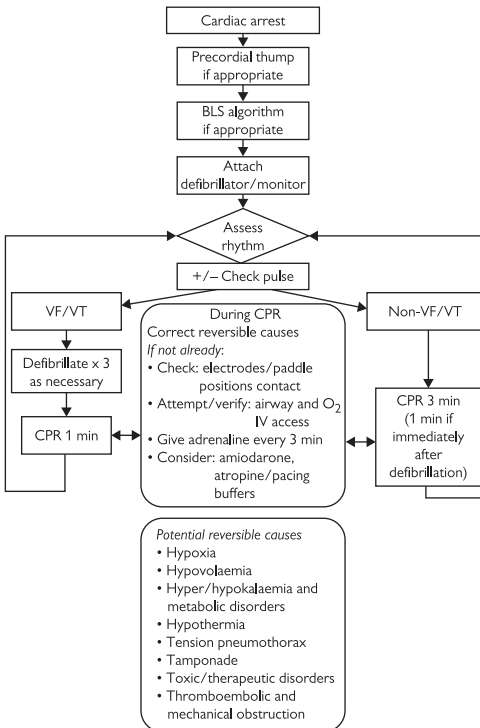


Fig. 1.3 Universal treatment algorithm (for further details, see the Resuscitation Council (UK) website <http://www.resus.org.uk>).

Acute coronary syndrome

Acute coronary syndrome (ACS) is an operational term used to describe a constellation of symptoms resulting from acute myocardial ischaemia. An ACS resulting in myocardial injury is termed an MI. ACS includes the diagnosis of unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). The term ACS is generally assigned by ancillary/triage personnel on initial contact with the patient. Guidelines for identification of ACS are summarized on  Non-ST-elevation myocardial infarction/unstable angina, pp. 46–7.

Definition

The current nomenclature divides ACS into two major groups, on the basis of delivered treatment modalities (see Fig. 1.4).

- STEMI: ACS where patients present with ischaemic chest discomfort and ST-segment elevation on ECG. This group of patients must undergo reperfusion therapy on presentation.
- NSTEMI and UA: ACS where patients present with ischaemic chest discomfort associated with transient or permanent non-ST-elevation ischaemic ECG changes. If there is biochemical evidence of myocardial injury, the condition is termed NSTEMI, and in the absence of biochemical myocardial injury, the condition is termed UA (see Fig. 1.4). This group of patients is not treated with thrombolysis.

Initial management of ACS

- All patients with suspected ACS should be placed in an environment with continuous ECG monitoring and defibrillation capacity.
- Give aspirin and clopidogrel (300mg PO of each if no contraindications), and do not give any intramuscular (IM) injections (causes a rise in total creatine kinase (CK) and risk of bleeding with thrombolysis/anticoagulation). There is some evidence that a loading dose of 600mg of clopidogrel achieves quicker platelet inhibition and should be considered for patients going to the cardiac cathlab for immediate percutaneous coronary intervention (PCI).

Immediate assessment should include:

- Rapid examination to exclude hypotension and note the presence of murmurs, and to identify and treat acute pulmonary oedema.
- Secure IV access.
- 12-lead ECG should be obtained and reported within 10min.
- Give high-flow oxygen (O_2) [initially only 28% if history of chronic obstructive pulmonary disease (COPD)].
- Diamorphine 2.5–10mg IV as required (PRN) for pain relief.
- Metoclopramide 10mg IV for nausea.
- Glyceryl trinitrate (GTN) spray two puffs (unless hypotensive).
- Take blood for:
 - Full blood count (FBC)/U&Es: supplement K^+ to keep it at 4–5mmol/L.
 - Glucose: may be acutely elevated post-MI, even in non-diabetics, and reflects a stress–catecholamine response, which may resolve without treatment.
 - Biochemical markers of cardiac injury (see Box 1.4).

- Lipid profile: total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides.
- Serum cholesterol and HDL remain close to baseline for 24–48h but fall thereafter and take ≥ 8 weeks to return to baseline.
- Portable CXR to assess cardiac size and for pulmonary oedema, and to exclude mediastinal enlargement.
- General examination should include peripheral pulses, fundoscopy, abdominal examination for organomegaly, and aortic aneurysm.
- Consider alternative diagnoses (see Box 1.1).

Box 1.1 Conditions mimicking pain in ACS

- Pericarditis.
- Dissecting aortic aneurysm.
- Pulmonary embolism (PE).
- Oesophageal reflux, spasm, or rupture.
- Biliary tract disease.
- Perforated peptic ulcer.
- Pancreatitis.

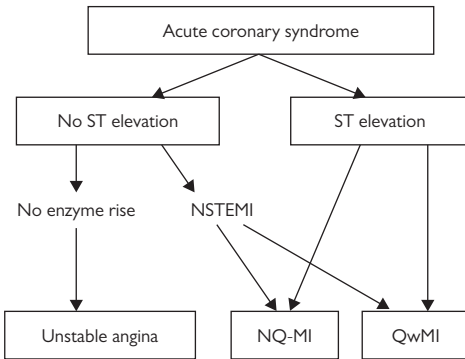


Fig. 1.4 Nomenclature of ACS. Patients with ACS may present with or without ST-elevation on the ECG. The majority of patients with ST-elevation (large arrows) ultimately develop Q-wave MI (QwMI), whereas a minority (small arrow) develop a non-Q-wave MI (NQ-MI). Patients without ST-elevation experience either UA or an NSTEMI, depending on the absence or presence of cardiac enzymes (e.g. troponin) detected in the blood.

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ST-elevation myocardial infarction (STEMI)

Patients with an ACS who have ST-segment elevation/left bundle branch block (LBBB) on their presenting ECG benefit significantly from immediate reperfusion and are treated as one group under the term STEMI.

Presentation

- Chest pain usually similar in nature to angina, but of greater severity and longer duration, and not relieved by sublingual (SL) GTN. Associated features include nausea and vomiting, sweating, breathlessness, and extreme distress.
- The pain may be atypical, such as epigastric, or radiate through to the back.
- Diabetics, the elderly, and hypertensives may suffer painless ('silent') infarcts and/or atypical infarction. Women and certain ethnic groups are more likely to have an atypical presentation. Features include breathlessness from acute pulmonary oedema, syncope or coma from arrhythmias, acute confusional states (mania/psychosis), diabetic hyperglycaemic crises, hypotension/cardiogenic shock, central nervous system (CNS) manifestations resembling stroke secondary to sudden reduction in cardiac output, and peripheral embolization.

Management

Diagnosis is normally made on presentation, followed by rapid stabilization to ensure prompt reperfusion therapy. This is in contrast to non-ST-elevation (NSTEMI)-ACS where the diagnosis may evolve over a period of 24–72h (➡ Non-ST-elevation myocardial infarction/unstable angina, pp. 46–7). The management principles of the various stages are outlined here and expanded on subsequently (also see Box 1.2).

- Stabilizing measures are generally similar for all ACS patients (➡ Acute coronary syndrome, pp. 10–11).
 - All patients with suspected STEMI should have *continuous ECG monitoring* in an area with full resuscitation facilities.
 - Patients should receive immediate *aspirin* 300mg PO and *clopidogrel* 300mg PO (if no contraindications), *analgesia*, and *O₂*.
 - Rapid examination to exclude hypotension and note the presence of murmurs, and to identify and treat acute pulmonary oedema. Examine for signs of aortic dissection [e.g. aortic regurgitation (AR) murmur, unequal blood pressure (BP) in the arms]. Right ventricular failure (RVF) out of proportion to left ventricular failure (LVF) suggests right ventricular (RV) infarction (➡ Right ventricular infarction, p. 28).
 - Blood for FBC, biochemical profile, markers of cardiac injury, lipid profile, and glucose, and portable CXR.
- *Diagnosis* must be made on the basis of history, ECG (ST-elevation/new LBBB), and biochemical markers of myocardial injury (NB If ECG changes diagnostic, reperfusion must not be delayed to wait for biochemical markers) (➡ STEMI: diagnosis 2, p. 16). Echocardiography (Echo) can be helpful to look for regional hypokinesia.
- *Treatment:*

- General medical measures (➡ STEMI: general measures, pp. 18–19)
- Reperfusion (➡ STEMI: reperfusion therapy (thrombolysis) 1, pp. 20–1).
- *All patients with STEMI should be admitted to the CCU.*
- *Discharge and risk prevention (➡ STEMI: predischarge risk stratification, pp. 30–1).*

Box 1.2 Factors associated with a poor prognosis

- Age >70 years.
- Previous MI or chronic stable angina.
- Anterior MI or RV infarction.
- LV failure at presentation.
- Hypotension (and sinus tachycardia) at presentation.
- Diabetes mellitus.
- Mitral regurgitation (acute).
- Ventricular septal defect.

STEMI: diagnosis 1

This is based on a combination of history, ECG, and biochemical markers of cardiac injury. In practice, history and ECG changes are normally diagnostic, resulting in immediate reperfusion/medical treatment. Biochemical markers of cardiac injury usually become available later and help reconfirm the diagnosis, as well as provide prognostic information (magnitude of rise).

ECG changes

(Also see Box 1.3.)

- *ST-segment elevation* occurs within minutes and may last for up to 2 weeks. ST-elevation of $\geq 2\text{mm}$ in adjacent chest leads and $\geq 1\text{mm}$ in adjacent limb leads is necessary to fulfil thrombolysis criteria. Persisting ST-elevation after 1 month suggests formation of LV aneurysm. Infarction site can be localized from ECG changes, as indicated in Table 1.1.
- *Pathological Q waves* indicate significant abnormal electrical conduction but are not synonymous with irreversible myocardial damage. In the context of a 'transmural infarction', they may take hours or days to develop and usually remain indefinitely. In the standard leads, the Q wave should be $\geq 25\%$ of the R wave and 0.04s in duration, with negative T waves. In the precordial leads, Q waves in V4 should be $>0.4\text{mV}$ (four small squares) and in V6 $>0.2\text{mV}$ (two small squares), in the absence of LBBB (QRS width $<0.1\text{s}$ or three small squares).
- *ST-segment depression* (ischaemia at distance) in a 2nd territory (in patients with ST-segment elevation) is secondary to ischaemia in a territory other than the area of infarction (often indicative of multi-vessel disease) or reciprocal electrical phenomena. Overall it implies a poorer prognosis.
- *PR-segment elevation/depression* and alterations in the contour of the P wave are generally indicative of atrial infarction. Most patients will also have abnormal atrial rhythms such as atrial fibrillation (AF)/flutter and wandering atrial pacemaker and atrioventricular (AV) nodal rhythms.
- *T-wave inversion* may be immediate or delayed and generally persists after the ST-elevation has resolved.
- *Non-diagnostic changes*, but the ones that may be ischaemic, include new LBBB or right bundle branch block (RBBB), tachyarrhythmias, transient tall peaked T waves or T-wave inversion, axis shift (extreme left or right), or AV block.

Box 1.3 Conditions that may mimic ECG changes of an STEMI

- LV or RV hypertrophy.
- LBBB or left anterior fascicular block.
- Wolff–Parkinson–White syndrome.
- Pericarditis or myocarditis.
- Cardiomyopathy (hypertrophic or dilated).
- Trauma to myocardium.
- Cardiac tumours (primary and metastatic).
- Pulmonary embolus.
- Pneumothorax.
- Intracranial haemorrhage.
- Hyperkalaemia.
- Cardiac sarcoid or amyloid.
- Pancreatitis.

Table 1.1 Localization of infarcts from ECG changes

Anterior	ST elevation and/or Q waves in V1–V4/V5
Anteroseptal	ST elevation and/or Q waves in V1–V3
Anterolateral	ST elevation and/or Q waves in V1–V6, I, and aVL
Lateral	ST elevation and/or Q waves in V5–V6 and T-wave inversion/ST elevation/Q waves in I and aVL
Inferolateral	ST elevation and/or Q waves in II, III, aVF, and V5–V6 (sometimes I and aVL)
Inferior	ST elevation and/or Q waves in II, III, and aVF
Inferoseptal	ST elevation and/or Q waves in II, III, aVF, and V1–V3
True posterior	Tall R waves in V1–V2 with ST depression in V1–V3 T waves remain upright in V1–V2 This can be confirmed with electrodes on the back for a posterior ECG. Usually occurs in conjunction with an inferior or lateral infarct
RV infarction	ST-segment elevation in the right precordial leads (V3R–V4R) Usually found in conjunction with inferior infarction. This may only be present in the early hours of infarction

STEMI: diagnosis 2

Biochemical markers of cardiac injury

Serial measurements evaluating a temporal rise and fall should be obtained to allow a more accurate diagnosis. CK and creatine kinase-muscle/brain (CK-MB) from a skeletal muscle source tend to remain elevated for a greater time period, in comparison to a cardiac source.

CK

- Levels twice the upper limit of normal are taken as being abnormal.
- Serum levels rise within 4–8h post-STEMI and fall to normal within 3–4 days. The peak level occurs at about 24h but may be earlier (12h) and higher in patients who have had reperfusion (thrombolysis or PCI); enzymes from the damaged muscle are ‘washed out’ of the infarcted area with restored circulation.
- False positive rates of ~15% occur in patients with alcohol intoxication, muscle disease or trauma, vigorous exercise, convulsions, IM injections, hypothyroidism, pulmonary embolism (PE), and thoracic outlet syndrome.

CK-MB isoenzyme is more specific for myocardial disease. Levels may be elevated despite a normal total CK. However, CK-MB is also present in small quantities in other tissues (skeletal muscle, tongue, diaphragm, uterus, and prostate), and trauma or surgery may lead to false positive results. If there is doubt about myocardial injury with CK-MB levels obtained, a cardiac troponin must be measured.

Cardiac troponins (TnT, TnI)

- Both TnI and TnT are highly sensitive and specific markers of cardiac injury.
- Serum levels start to rise by 3h post-MI, and elevation may persist up to 7–14 days. This is advantageous for diagnosis of late MI.
- In most STEMI cases, the diagnosis can be made using a combination of the clinical picture and serial CK/CK-MB levels. In the event of normal CK-MB levels and suspected non-cardiac sources of CK, troponins can be used.
- Troponins can also be elevated in non-ischaemic myocyte damage such as myocarditis, cardiomyopathy, and pericarditis.

Other markers

There are multiple other markers, but with increasing clinical availability of troponins, measurements are not recommended. These include aspartate transaminase (AST) (rise 18–36h post-MI) and lactate dehydrogenase (LDH) (rise 24–36h post-MI).

The time course of the various markers is seen in Fig. 1.5.

For key points on non-ACS causes of raised troponin, see Box 1.4.

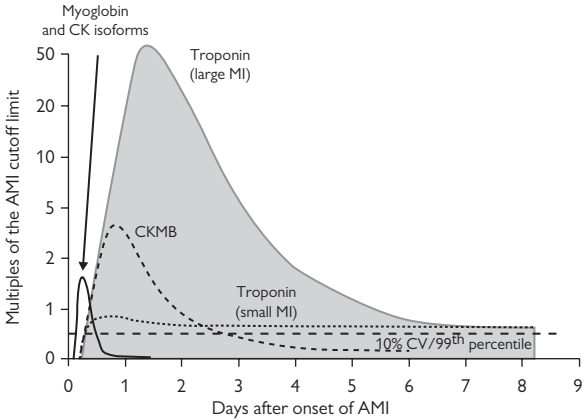


Fig. 1.5 Timing of biomarkers after myocardial infarction.

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Box 1.4 Key points: non-ACS causes of raised troponin

- Troponin is a sensitive marker of myocyte damage.
- Raised troponin is not specific to thrombotic coronary artery occlusion.
- Measurement of troponin levels in broad populations with low pretest probability of thrombotic disease greatly reduces its positive predictive value for NSTEMI.
- Causes of elevated troponin other than acute thrombotic coronary artery occlusion include:
 - Sepsis
 - Myocarditis/pericarditis
 - PE
 - Cardiac failure
 - Renal failure
 - Stroke
 - Cardiac contusion
 - Tachycardia.
- In patients with raised troponin, determine the pretest probability of coronary artery disease (chest pain, risk factors for ischaemic heart disease, ischaemic ECG changes, wall motion abnormalities on echocardiography).
- Patients with a low pretest probability of coronary heart disease/ACS are unlikely to benefit from a treatment aimed at coronary artery thrombosis (i.e. antithrombotic/antiplatelet therapy, coronary angiography and revascularization). In these patients identify and treat the underlying cause of raised troponin (see earlier list).

STEMI: general measures

(See Box 1.6.)

Immediate stabilizing measures

These are as outlined in  Acute coronary syndrome, pp. 10–11.

Control of cardiac pain

- *Diamorphine 2.5–10mg IV* is the drug of choice and may be repeated to ensure adequate pain relief, unless evidence of emerging toxicity (hypotension, respiratory depression). Nausea and vomiting should be treated with metoclopramide (10mg IV) or a phenothiazine.
- O_2 to be administered at 2–5L/min if O_2 saturation <90%. Hypoxaemia is frequently seen post-MI due to ventilation–perfusion abnormalities secondary to LVF. In patients with refractory pulmonary oedema, continuous positive airways pressure (CPAP) or via formal ET intubation may be necessary. Beware of carbon dioxide (CO_2) retention in patients with COPD.
- *Nitrates* may lessen pain and can be given, providing that the patient is not hypotensive (SL or IV). They need to be used cautiously in inferior STEMI, especially with RV infarction, as venodilation may impair RV filling and precipitate hypotension. Nitrate therapy has no effect on mortality (ISIS-4).

Correction of electrolytes

Both low potassium and magnesium may be arrhythmogenic and must be supplemented, especially in the context of arrhythmias.

Strategies to limit infarct size

β -blockade, angiotensin-converting enzyme inhibitor (ACEI), and reperfusion.

Beta-blockade

- Early β -blockade in limiting infarct size, reducing mortality, and early malignant arrhythmias. All patients (including primary PCI and thrombolysis patients) should have early β -blockade, but those with the following features will benefit most:
 - Hyperdynamic state (sinus tachycardia, $\uparrow$ BP)
 - Ongoing or recurrent pain/reinfarction
 - Tachyarrhythmias such as AF.
- Absolute contraindications: HR <60bpm, systolic BP (SBP) <100mmHg, moderate to severe heart failure, AV conduction defect, severe airways disease.
- Relative contraindications: asthma, current use of calcium channel blocker and/or β -blocker, severe peripheral vascular disease with critical limb ischaemia, large inferior MI involving the RV.
- Use a short-acting agent IV initially (metoprolol 1–2mg at a time, repeated at 1- to 2-min intervals to a maximum dose of 15–20mg) under continuous ECG and BP monitoring. Aim for a pulse rate of 60bpm and SBP of 100–110mmHg. If haemodynamic stability continues 15–30min after last IV dose, start metoprolol 50mg three times daily (tds). Esmolol is an ultra-short-acting IV β -blocker, which may be tried if there is concern whether the patient will tolerate β -blockers.

ACEIs

After receiving aspirin, β -blockade (if appropriate), and reperfusion, all patients with STEMI/LBBB infarction should receive an ACEI within the first 24h of presentation.

- Patients with high-risk/large infarcts, particularly with an anterior STEMI, a previous MI, heart failure, or impaired LV function on imaging (Echo) or those who are elderly will benefit most.
- The effect of ACEIs appears to be a class effect—use the drug with which you are familiar [e.g. ramipril 1.25mg once daily (od)].

STEMI: reperfusion by primary percutaneous coronary intervention

Time is of the essence for reperfusion, and each institution should have its recommended protocol. It is imperative that there are no delays in both the decision-making and implementation processes for reperfusion. If primary PCI is chosen, one telephone call should ensure a rapid response.

Primary PCI

- Primary PCI is the current gold standard reperfusion strategy for treatment of STEMI.
- Primary PCI requires significant coordination between the emergency services, community hospitals, and invasive centres. It must only be performed if:
 - A primary PCI programme is available *and*
 - The patient presents to an invasive centre and can undergo catheterization without delay.

Indications for primary PCI

- All patients with chest pain and ST-segment elevation or new LBBB fulfil primary PCI criteria (compare with indications for thrombolysis).
- This will include a group of patients where ST-segment elevation may not fulfil the thrombolysis criteria.
- In general, patients in whom thrombolysis is contraindicated should be managed by primary PCI. Cases where there is a significant risk of bleeding must be managed individually.

Outcome in primary PCI

- Data from >10 large randomized trials demonstrate a superior outcome in patients with STEMI who are treated with primary PCI, in comparison to thrombolysis.
- There is a significant short-term, as well as long-term, reduction in mortality and major adverse cardiac events (MACE) (death, non-fatal reinfarction, and non-fatal stroke) in STEMI patients treated with primary PCI. Furthermore, primary PCI patients have overall better LV function, a higher vessel patency rate, and less recurrent myocardial ischaemia.
- Multiple studies (including PRAGUE-2 and DANAMI-2) have also demonstrated that interhospital transportation for primary PCI (community hospital to invasive centre) is safe and primary PCI continues to remain superior to thrombolysis despite the time delays involved.

Complications

- These include bleeding from arterial puncture site, stroke, recurrent infarction, need for emergency coronary artery bypass graft (CABG), and death, which are similar to high-risk PCI cases (1%).
- The best results are obtained from high-volume centres with experience of primary PCI.

- Each primary PCI centre will have its own policy for management of cases, including the use of low-molecular weight heparin (LMWH)/unfractionated heparin (UFH) and antiplatelet agents (e.g. IIb/IIIa). It is generally accepted that, in the acute phase, only the 'culprit' lesion(s)/vessel(s) will be treated. The pattern of disease in the remainder of the vessels will determine whether total revascularization should be performed as an inpatient or elective case at some stage in the future.
- STEMI patients treated with primary PCI can be discharged safely within 72h of admission without the need for further risk stratification.
- Primary PCI is more cost-effective in the long term, with significant savings from fewer days in hospital, a lower need for readmission, and less heart failure.
- Post-discharge care, secondary prevention, and rehabilitation remain identical to other MI cases.

Rescue PCI

As an adjunct to thrombolysis, PCI should be reserved for patients who remain symptomatic post-thrombolysis (failure to reperfuse) or develop cardiogenic shock (➡ Cardiogenic shock, pp. 44–5). We recommend all patients who do not settle post-thrombolysis [ongoing symptoms and ongoing ST elevation with/without symptoms (<50% resolution of ST elevation at 90min post-lysis)] should be discussed with the local cardiac centre for urgent catheterization and revascularization.

For key points on STEMI, see Boxes 1.5 and 1.6.

Box 1.5 Key points: STEMI

- Rapid reperfusion is the cornerstone of management of STEMI.
- Reperfusion is marked by normalization of ST segments on ECG.
- The best long-term outcome is achieved with primary PCI.
- Thrombolysis may be used if primary PCI is not available.

Box 1.6 Management key points: STEMI

- Aspirin, clopidogrel, O₂, continuous ECG monitoring.
- Analgesia: diamorphine (+ metoclopramide), GTN (monitor BP).
- Reperfusion therapy without delay: primary PCI (gold standard) or thrombolysis.
- If primary PCI not available: carefully and rapidly assess indications and contraindications to thrombolysis.
- IV heparin should be used with rtPA (and its derivatives), but not with SK.
- Early short-acting β -blockers, e.g. metoprolol (if not contraindicated).
- Correct low potassium and magnesium.
- ACEI within the first 24h of presentation.

STEMI: reperfusion therapy (thrombolysis) 1

Reperfusion occurs in 50–70% of patients who receive thrombolysis within 4h of onset of pain (compared with ~20% of controls). As with primary PCI, thrombolysis also results in reduction in mortality, LV dysfunction, heart failure, cardiogenic shock, and arrhythmias. However, the magnitude of the benefits obtained is smaller. Furthermore, patients must undergo cardiac catheterization to delineate their coronary anatomy before revascularization (achieved at the same time with primary PCI). Time is, once again, of paramount importance and thrombolysis should be administered as soon as possible (see Box 1.5).

Indications for thrombolysis

- Typical cardiac pain within previous 12h and ST elevation in two contiguous ECG leads (>1mm in limb leads or >2mm in V1–V6).
- Cardiac pain with new/presumed new LBBB on ECG.
- If ECG is equivocal on arrival, repeat at 15- to 30-min intervals to monitor progression.
- Thrombolysis should not be given if the ECG is normal or if there is isolated ST depression (must exclude true posterior infarct).
- Remember patients with diabetes may present with dyspnoea or collapse without chest pain. Look for new ST elevation on the ECG.
- True posterior infarction presents with ST depression in anterior chest leads (V1–V3), often with ST changes in inferior leads as well. If suspected, administer thrombolysis.

Timing of thrombolysis

- Greatest benefit is achieved with early thrombolysis (especially if given within 4h of onset of first pain).
- Patients presenting between 12 and 24h from onset of pain should be thrombolysed if there are any persisting symptoms and/or ST-segment elevation on the ECGs.
- Patients presenting within 12–24h from the onset of pain whose clinical picture and ECGs appear to have settled should be managed initially as an NSTEMI, followed by early catheterization.

Choice of thrombolytic agent

- This is partly determined by the local thrombolysis strategy.
- Allergic reactions and episodes of hypotension are greater with streptokinase (SK).
- Bolus agents are easier and quicker to administer, with a decrease in drug errors, in comparison to first-generation infusions.
- Recombinant tissue plasminogen activator (rtPA) has a greater reperfusion capacity and a marginally higher 30-day survival benefit than SK, but an ↑ risk of haemorrhage.
- More recent recombinant plasminogen activator (rPA) derivatives have a higher 90-min TIMI-III flow rate, but similar 30-day mortality benefit to rtPA.

- An rtPA derivative should be considered for any patient with:
 - Large anterior MI, especially if within 4h of onset
 - Previous SK therapy or recent streptococcal infection
 - Hypotension (SBP <100mmHg)
 - Low risk of stroke (age <55 years, SBP <144mmHg)
 - Reinfarction where immediate PCI facilities are not available.

The characteristics of the major thrombolytic agents are given in Box 1.7.

Patients who gain greatest benefit from thrombolysis

- Anterior infarct.
- Marked ST elevation.
- Age >75 years.
- Impaired LV function or LBBB, hypotensive.
- SBP <100mmHg.
- Patients presenting within 1h of onset of pain.

Box 1.7 Doses and administration of thrombolytic agents

Streptokinase

- Give as 1.5MU in 100mL of normal saline IV over 1h.
- There is no indication for routine heparinization after SK administration, as there is no clear mortality benefit and there is a small increase in the risk of haemorrhage.

Alteplase (rtPA)

- The GUSTO trial suggested that 'front-loaded' or accelerated rtPA is the most effective dosage regimen.
- Give a 15-mg bolus IV, then 0.75mg/kg over 30min (not to exceed 50mg), then 0.5mg/kg over 60min (not to exceed 35mg).
- This should be followed by IV heparin (see text).

Retepase

- Give two IV bolus doses of 10U, 10min apart.

Tenecteplase

- Give as an injection over 10s at 30–50mg, according to bodyweight (500–600 micrograms/kg).
- Maximum dose is 50mg.

APSAC (anistreplase)

- Give as an IV bolus of 30mg over 2–5min.

STEMI: thrombolysis 2

Complications of thrombolysis

- Bleeding is seen in up to 10% of patients. Most are minor at sites of vascular puncture. Local pressure is sufficient, but occasionally transfusion may be required. In extreme cases, SK may be reversed by tranexamic acid (10mg/kg slow IV infusion).
- Hypotension during the infusion is common with SK. Lay the patient supine, and slow/stop the infusion until the BP rises. Treatment with cautious (100–500mL) fluid challenges may be required, especially in inferior/RV infarction. Hypotension is not an allergic reaction and does not warrant treatment as such.
- Allergic reactions are common with SK and include low-grade fever, rash, nausea, headaches, and flushing. Give hydrocortisone 100mg IV, with chlorphenamine 10mg IV.
- Intracranial haemorrhage is seen in ~0.3% of patients treated with SK and ~0.6% of those with rtPA.
- Reperfusion arrhythmias (most commonly a short, self-limiting run of idioventricular rhythm) may occur as the metabolites are washed out of the ischaemia tissue (➡ Ventricular tachyarrhythmia post-MI, p. 40; ➡ Bradyarrhythmias and indications for pacing, p. 41; ➡ Bradyarrhythmias post-MI, p. 41).
- Systemic embolization may occur from lysis of thrombus within the left atrium (LA), left ventricle (LV), or aortic aneurysm.

Absolute contraindications to thrombolysis

- Active internal bleeding.
- Suspected aortic dissection.
- Recent head trauma and/or intracranial neoplasm.
- Previous haemorrhagic stroke at any time.
- Previous ischaemic stroke within the past 1 year.
- Previous allergic reaction to a fibrinolytic agent.
- Trauma and/or surgery within the past 2 weeks at risk of bleeding.

Relative contraindications to thrombolysis

- Trauma and/or surgery >2 weeks previously.
- Severe uncontrolled hypertension (BP >180/110) with/without treatment.
- Non-haemorrhagic stroke over 1 year ago.
- Known bleeding diathesis or current use of anticoagulation within therapeutic range [international normalized ratio (INR) 2 or over].
- Significant liver or renal dysfunction.
- Prolonged (>10min) of CPR.
- Prior exposure to SK (especially previous 6–9 months).
- Pregnancy or postpartum.
- LP (lumbar puncture) within previous 1 month.
- Menstrual bleeding or lactation.
- History of chronic severe hypertension.
- Non-compressible vascular punctures (e.g. subclavian central venous lines).
- Proliferative diabetic retinopathy (risk of intraocular bleed).

Surgery for acute STEMI

Emergency surgical revascularization (CABG) cannot be widely applied to patients who suffer an MI outside of the hospital. CABG in uncomplicated STEMI patients after 6h from presentation is contraindicated secondary to significant haemorrhage into areas of infarction. Unstable patients have a very high perioperative mortality.

CABG in the context of an acute STEMI is of value in the following situations:

- Persistent or recurrent chest pain despite thrombolysis/primary PCI.
- High-risk coronary anatomy on catheterization [left main stem (LMS), left anterior descending artery (LAD) ostial disease].
- Complicated STEMI [acute mitral regurgitation (MR), ventricular septal defect (VSD)].
- Patients who have undergone successful thrombolysis, but with surgical coronary anatomy on catheterization.
- Patients known to have surgical coronary anatomy on catheterization performed prior to admission with STEMI.

STEMI: additional measures

Low-molecular weight and unfractionated heparin

LMWH

- There are trial data for the use of LMWH and thrombolysis [e.g. enoxaparin 30mg IV bolus, then 1mg/kg subcutaneously (SC) every 12h].
- LMWH can be used at a prophylactic dose to prevent thromboembolic events in patients slow to mobilize, as an alternative to UFH.

UFH

- There is no indication for 'routine' IV heparin following SK.
- IV heparin [4000U/max. IV bolus, followed by 1000U/h max. adjusted for an activated partial thromboplastin time (APTT) ratio of 1.5–2.0 times control] should be used routinely, following rtPA and its derivatives, for 24–48h.

Clopidogrel (and other antiplatelets, e.g. prasugrel, ticagrelor)

- The addition of clopidogrel to aspirin and fibrinolytics has been shown to reduce the incidence of death or MACE by 20% at 30 days.
- If coronary stents are deployed, the patient should remain on dual anti-platelet therapy (DAPT) ideally for 12 months, as for patients with NSTEMI.

Glycoprotein IIb/IIIa inhibitors

- There does not appear to be any benefit of glycoprotein (GP) IIb/IIIa in combination with full- or reduced-dose thrombolytics in STEMI.
- GP IIb/IIIa inhibitors are recommended routinely in the context of STEMI patients treated with primary PCI. Best data are with abciximab.
- They can also be used in the context of rescue PCI, subsequent to failed thrombolysis, although there is a greater risk of bleeding. Each case must be judged on its merits.

Magnesium

- Earlier trials giving Mg^{2+} before or with thrombolytics showed some benefit in mortality. ISIS-4 showed no benefit from the routine use of IV Mg^{2+} post-MI. However, Mg^{2+} was given late (6h) after thrombolysis, by which time its protective effect on reperfusion injury may have been lost. Trials are ongoing.
- Current accepted role for Mg^{2+} is confined to Mg^{2+} -deplete patients and patients with reperfusion, supraventricular, and ventricular arrhythmias.
- Dose: 8mmol in 20mL of 5% glucose over 20min, followed by 65mmol in 100mL of 5% glucose over 24h (contraindications: serum creatinine >300 micromol/L, third-degree AV block).

Calcium antagonists

- Best avoided, especially in the presence of LV impairment.
- Diltiazem and verapamil started after day 4–5 in post-MI patients with normal LV function have a small beneficial effect.
- Amlodipine is safe to be used in patients with poor LV post-MI.
- Nifedipine has been shown to increase mortality and should be avoided.

Digoxin

- Has little role in the management of an acute STEMI and heart failure complicating an acute MI.
- Can be used safely in the management of arrhythmias and heart rate (HR).

Right ventricular infarction

- RV infarction results in elevated right-sided pressures [(right atrial (RA), right ventricular end-diastolic pressure (RVEDP)] and low left-sided pressures [BP, cardiac output (CO)].
- It is common in inferior STEMI.

Diagnosis

- *Clinical*: signs of right heart failure ($\uparrow$ JVP, Kussmaul's sign, pulsus paradoxus), with absence of pulmonary oedema, in the context of a low output state ($\downarrow$ BP, cold peripheries).
- *ECG*: in patients with inferior STEMI, a 0.1mV (>1 mm) ST-segment elevation in any one of leads V4R–V6R is highly sensitive and specific for RV infarction. See Fig. 1.6 for different ECG patterns identified in right-sided precordial leads. Changes may be transient and present in the early stages only.
- *Echo*: looking for RV dilatation and wall motion abnormalities.

Management

- Aim to maintain a high RV preload:
 - Initially give 1–2L of colloid rapidly.
 - Avoid use of nitrates and diuretics, as they reduce preload and can worsen hypotension.
 - In patients requiring pacing, AV synchrony must be maintained to ensure maximal CO (atrial and ventricular wires).
 - Cardiovert any arrhythmias [supraventricular tachycardia (SVT), AF/flutter, or ventricular rhythms].
- Reduce afterload:
 - This is particularly important if there is concomitant LV dysfunction.
 - Insert intra-aortic balloon pump (IABP).
 - Arterial vasodilators (sodium nitroprusside, hydralazine) or ACEIs can be used with caution.
- Inotropic support should ideally be avoided and used only if all other measures fail to restore the haemodynamic status.
- Reperfusion of the right coronary artery (RCA) (PCI or thrombolysis) has been demonstrated to improve RV function and reduce mortality.

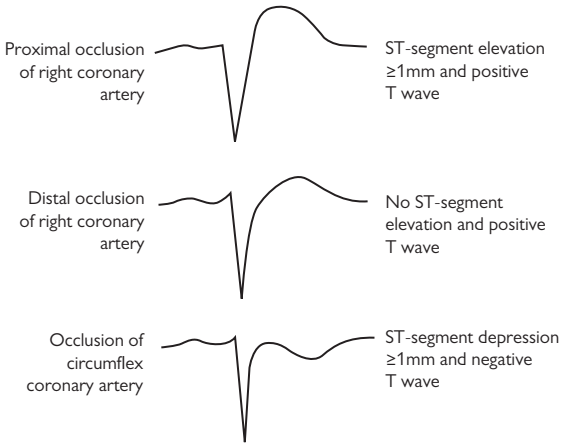


Fig. 1.6 ST elevation and T-wave configuration in lead V4R in inferoposterior acute MI. Proximal occlusion of the RCA produces ST elevation of $\geq 1\text{mm}$ and a positive T wave. Distal occlusion is characterized by a positive T wave, but no ST elevation. Occlusion of the circumflex artery produces a negative T wave and ST depression of at least 1mm.

From *N Engl J Med*, Wellens HJ, 'The value of the right precordial leads of the electrocardiogram', 340, 381–3. Copyright © 1999 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

STEMI: predischARGE risk stratification

It is important to identify the subgroup of patients who have a high risk of reinfarction or sudden death. They should undergo coronary angiography, with a view to revascularization prior to discharge (if not treated with primary PCI), and/or electrophysiological investigations as necessary (see Fig. 1.7).

Primary PCI group

- STEMI patients treated with primary PCI are at a much lower risk of developing post-MI complications.
- There is ongoing debate about whether patients treated with primary PCI should have total revascularization as an inpatient or whether this can be achieved after functional testing on an outpatient basis. Follow your local policy.
- Patients who should have electrophysiological assessment prior to discharge are listed under  Electrophysiological study, p. 30.

Thrombolysis group

Patients treated with thrombolysis should be risk-stratified prior to discharge, and high-risk patients should have inpatient (or early outpatient) angiography. High-risk patients include those with:

- Significant post-infarct angina or UA.
- Positive exercise test (modified Bruce protocol) with angina, >1mm ST depression, or fall in BP.
- Cardiomegaly on CXR, poor LV function on Echo [ejection fraction (EF) <40%].
- Documented episodes of regular ventricular extrasystoles (VEs) and VT 24h post-infarction.
- Frequent episodes of silent ischaemia on Holter monitoring.

Electrophysiological study

All STEMI patients with (1) non-sustained VT and documented EF <40% or (2) sustained/pulseless VT/VF (regardless of EF) should undergo electrophysiological testing prior to discharge (MADIT and MUSTT trials), with a view to defibrillator implantation.

Discharge and secondary prevention

- Length of hospital stays in uncomplicated patients. The thrombolysis group needs to undergo risk stratification prior to discharge and tends to have a mean hospital stay of 5–7 days. The primary PCI group has a shorter hospital stay of between 3 and 4 days.
- Prior to discharge, an agreed plan between patient (and patient's family) and physician is necessary to address modifiable risk factors, beneficial medication, and rehabilitation programme.
- Modifiable risk factors include:
 - Management of lipids and use of statins
 - Detection and treatment of diabetes
 - Ensuring BP is adequately controlled
 - Counselling to discontinue smoking
 - Advice on a healthy diet and weight loss.

- It is vital patients understand the medical regimen and, in particular, the importance of long-term 'prognostic medication'. Unless there are contraindications, all patients should be on a minimum of:
 - Aspirin 75mg od (if true allergy, use clopidogrel 75mg od alone)
 - Clopidogrel 75mg od (for 12 months)
 - ACEI at the recommended dosage
 - Statin at the recommended dosage
 - The role of long-term formal anticoagulation is controversial.
- All patients must be offered a cardiac rehabilitation programme.

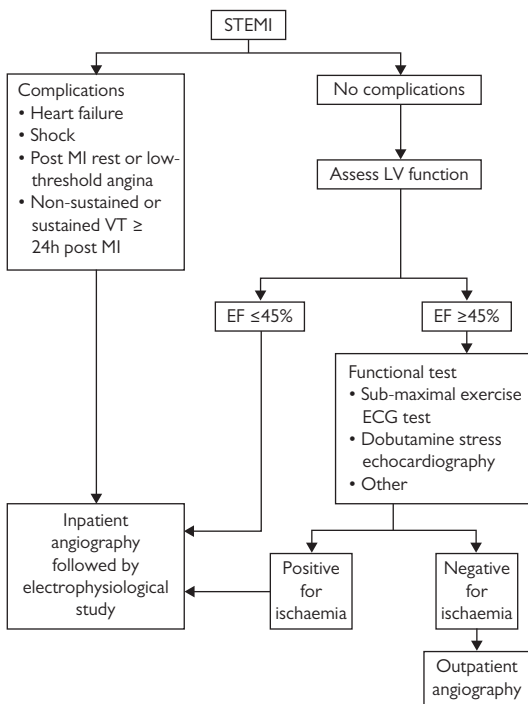


Fig. 1.7 Suggested strategy post-STEMI in patients who have undergone thrombolysis to determine the need for inpatient angiography/electrophysiological studies.

Source: data from Antman EM (2000). *Cardiovascular Therapeutics*, 2nd edn. Saunders, Philadelphia, PA.

STEMI: complications

Complications

- Continuing chest pain.
- Fever.
- New systolic murmur: VSD, acute MR, or pericarditis.
- Arrhythmia: VT, AV block ectopics, and bradycardia.
- Pump failure: hypotension, cardiac failure, and cardiogenic shock.

Complications are encountered more commonly in patients post-STEMI but can also be found in NSTEMI patients (➡ Non-ST-elevation myocardial infarction/unstable angina, pp. 46–7). In NSTEMI patients, complications are more common where multiple cardiac events have occurred.

Further chest pain

- Chest pain post-MI is not necessarily angina. A careful history is needed to characterize the pain. If there is doubt about the aetiology of the pain in the absence of ECG changes, stress/thallium imaging may aid diagnosis.
- A bruised sensation and musculoskeletal pain are common in the first 24–48h, especially in patients who have received CPR or repeated direct current (DC) shock. Use topical agents for skin burns.
- *Recurrent infarction* is an umbrella term including both extension of infarction in the original territory and repeated infarct in a 2nd territory.
 - Usually associated with recurrent ST elevation.
 - If cardiac enzymes are not yet back to normal, a significant change is a 2-fold rise above the previous nadir.
 - Patients should ideally undergo immediate PCI. Thrombolysis is an alternative, but a less attractive, approach. Standard thrombolysis criteria must be met (➡ STEMI: reperfusion therapy (thrombolysis) 1, pp. 22–3). Bleeding is a risk (NB SK should not be used on a 2nd occasion).
- *Post-infarction* angina (angina developing within 10 days of MI) should be treated with standard medical therapy. All patients with angina prior to discharge should undergo cardiac catheterization and revascularization as an inpatient.
- *Pericarditis* presents as sharp, pleuritic, and positional chest pain, usually 1–3 days post-infarct. It is more common with STEMI. A pericardial friction rub may be audible. ECG changes are rarely seen. Treat with high-dose aspirin [600mg four times daily (qds) PO], covering with a proton pump inhibitor (PPI) (e.g. lansoprazole 30mg od PO). Other NSAIDs have been associated with a higher incidence of LV rupture and ↑ coronary vascular resistance and are probably best avoided.
- *Pericardial effusion* is more common with anterior MI, especially if complicated by cardiac failure. Tamponade is rare and the result of ventricular rupture and/or haemorrhagic effusions. Detection is with a combination of clinical features and Echo. Most small effusions resolve gradually over a few months, with no active intervention.

- *Pulmonary thromboembolism* can occur in patients with heart failure and prolonged bed rest. Routine use of prophylactic LMWH and UFH, combined with early mobilization, has a reduced incidence of PE. Sources include lower limb veins and/or the RV (➡ Pulmonary embolism (PE): assessment, p. 126).
- *Fever* may be seen and peaks 3–4 days post-MI. It is associated with an elevated white cell count (WCC) and raised C-reactive protein (CRP). Other causes of fever should be considered—infection, thrombophlebitis, venous thrombosis, drug reaction, and pericarditis.

Ventricular septal defect post-myocardial infarction (MI)

- Classically seen 24h (highest risk) to 10 days post-MI and affects 2–4% of cases.
- *Clinical features* include rapid deterioration, with a harsh pan-systolic murmur (maximal at the lower left sternal edge), poor perfusion, and pulmonary oedema. The absence of a murmur in the context of a low output state does not rule out a VSD.

Diagnosis

- Echocardiography: the defect may be visualized on two-dimensional (2D)-Echo, and colour flow Doppler shows the presence of left-to-right shunt. Anterior infarction is associated with apical VSD, and inferior MI with basal VSD. Failure to demonstrate a shunt on Echo does not exclude a VSD.
- PA catheter (especially in the absence of Echo or inconclusive Echo results): a step-up in O₂ saturation from RA to RV confirms the presence of a shunt, which may be calculated by:

$$Q_p:Q_s = \frac{(\text{Art sat} - \text{RA sat})}{(\text{Art sat} - \text{PA sat})}$$

where Q_p = pulmonary blood flow; Q_s = systemic blood flow.

- Cardiovascular magnetic resonance imaging (MRI) can visualize the VSD but also allow for accurate calculation of the Q_p:Q_s.

Management

Stabilization measures are all temporizing until definitive repair can take place. Hypotension (➡ Hypotension and shock post-MI, p. 42) and pulmonary oedema (➡ Hypotension and shock post-MI, p. 42) should be managed as described elsewhere. Important principles are given here:

- Invasive monitoring (PA catheter and arterial line) to dictate haemodynamic management. RA and pulmonary capillary wedge pressure (PCWP) dictate fluid administration or diuretic use. CO, mean arterial pressure (MAP), and arterial resistance determine the need for vasodilator therapy.
- If SBP >100mmHg, cautious use of vasodilator therapy, generally with nitroprusside, will lower the systemic vascular resistance (SVR) and reduce the magnitude of the shunt. Nitrates will cause venodilation and increase the shunt and should be avoided. Not to be used with renal impairment.
- Inotropes if severely hypotensive (initially dobutamine, but adrenaline may be required, depending on haemodynamic response). Increasing systemic pressure will worsen shunt.
- Consider IABP in most cases.
- Liaise with surgeons early for possible repair. Operative mortality is high (20–70%), especially in the context of perioperative shock, inferoposterior MI, and RV infarction. Current recommendations are for high-risk early surgical repair, combined with CABG ± mitral valve (MV) repair/replacement.

- If the patient has been weaned off pharmacological and/or mechanical support, it may be possible to postpone surgery for 2–4 weeks to allow for some level of infarct healing. Patients should ideally undergo catheterization prior to surgical repair to ensure culprit vessel(s) are grafted.
- Closure of the VSD with catheter placement of an umbrella-shaped device (Amplatzer™) has been reported to stabilize critically ill patients until definitive repair is possible.

Acute mitral regurgitation post-MI

- MR due to ischaemic papillary muscle dysfunction or partial rupture is seen 2–10 days post-MI. Complete rupture causes torrential MR and is usually fatal.
- Presentation is acute-onset, severe breathlessness, with hypoxia, acute pulmonary oedema, diaphoresis, and rapid deterioration.
- More commonly associated with inferior MI (posteromedial papillary muscle) than anterior MI (anterolateral papillary muscle).
- 'Silent MR' is quite frequent and must be suspected in any post-MI patient with unexplained haemodynamic deterioration.
- Diagnosis is by Echo. In severe MR, PA catheterization will show a raised pressure, with a large v wave on the PCWP.

Management

- ⚡ Acute mitral regurgitation, pp. 120–1.)
- Treatment with vasodilators, generally nitroprusside, should be started as early as possible once haemodynamic monitoring is available. IABP could also be considered.
- Mechanical ventilation may be necessary.
- Liaise with surgeons early for possible repair or replacement.

Pseudoaneurysm and free wall rupture

- Demonstrated in up to 6% of STEMI patients and leads to sudden death in two-thirds.
- A proportion present subacutely with cardiogenic shock, allowing time for intervention.
- Diagnosis of subacute cases can be made on a combination of clinical features of pericardial effusion, tamponade, and Echo.
- Patients who have undergone early thrombolysis have a lower chance of wall rupture.
- Stabilization of the patient follows similar lines to cardiogenic shock (⚡ Cardiogenic shock, pp. 44–5). Case must be discussed with surgeons immediately, with a view to repair.

Cocaine-induced MI

- The incidence of cocaine-induced MI, LV dysfunction, and arrhythmias are on the increase (see Box 1.8).
- It has been estimated that 14–25% of young patients presenting to urban emergency departments with non-traumatic chest pain may have detectable levels of cocaine and its metabolites in their circulation. Of this group, 6% have enzymatic evidence of MI (figures are from the United States).
- Most patients are young, non-white, ♂ cigarette smokers, without other risk factors for IHD.

Diagnosis

- Can be difficult and must be suspected in any young individual with chest discomfort at low risk of developing OHD.
- Chest pain occurs most commonly within 12h of cocaine use. Effects can return up to 24–36h later, secondary to long-lasting active metabolites.
- ECG is abnormal, with multiple non-specific repolarization changes in up to 80% of cases, and ~40% may have diagnostic changes of STEMI qualifying for reperfusion therapy (➡ STEMI: diagnosis 1, p. 14).
- *Biochemical markers of cardiac injury* can be misleading, as most patients will have elevated CK levels secondary to rhabdomyolysis. TnT and TnI are vital to confirm myocardial injury.

Management

General measures

- These are the same as for anyone presenting with MI. High-flow O₂ 5–10L, unless there is a contraindication; analgesia; aspirin 75mg od.
- GTN: to be given at high doses as IV infusion (>10mg/h final levels) and dose titrated to symptoms and haemodynamic response (➡ STEMI: general measures, pp. 18–19).
- Benzodiazepines: are critical to reduce anxiety and tachycardia.

Second-line agents

- *Verapamil* is given in high doses and has the dual function of reducing cardiac workload, hence restoring O₂ supply and demand, as well as reversing coronary vasoconstriction. Should be given cautiously as 1- to 2-mg IV bolus at a time (up to 10mg total), with continuous haemodynamic monitoring. This should be followed by a high-dose oral preparation to cover the 24-h period for at least 72h after the last dose of cocaine (80–120mg PO tds).
- *Phentolamine* is an α -adrenergic antagonist and readily reverses cocaine-induced vasoconstriction (2–5mg IV and repeated if necessary). It can be used in conjunction with verapamil.
- *Labetalol* has both α - and β -adrenergic activity and can be used after verapamil and phentolamine if the patient remains hypertensive. It is effective in lowering cocaine-induced hypertension but has no effect on coronary vasoconstriction.

- *Reperfusion therapy*: evidence for use of thrombolysis is limited and generally associated with poor outcome secondary to hypertension-induced haemorrhagic complications. If the patient fails to settle after implementing first-line measures, verapamil, and phentolamine, they should undergo immediate coronary angiography, followed by PCI if appropriate (evidence of thrombus/vessel occlusion). In the event that angiography is not available, thrombolytic therapy can be considered.

Caution

β -blockers must be avoided. They exacerbate coronary vasoconstriction by allowing unopposed action of the adrenergic receptors.

Box 1.8 Pathogenesis and other complications of cocaine-induced MI

Pathogenesis

- The cause of myocardial injury is multifactorial, including an increase in O_2 demand ($\uparrow$ HR, $\uparrow$ BP, $\uparrow$ contractility) in the context of a decrease in supply caused by a combination of inappropriate vasoconstriction (in areas of minor atheroma), enhanced platelet aggregation, and thrombus formation.
- The effects can be delayed, as the metabolites of cocaine are potent active vasoconstrictors and can remain in the circulation for up to 36h (or longer), resulting in a recurrent wave of symptoms.

Other complications

- *Cocaine-induced myocardial dysfunction* is multifactorial and includes MI, chronic damage secondary to repetitive sympathetic stimulation (as in pheochromocytoma), myocarditis secondary to cocaine impurities/infection, and unfavourable changes in myocardial/endothelial gene expression.
- *Cocaine-induced arrhythmias* include both atrial and ventricular tachyarrhythmias, as well as asystole and heart block—see post-MI arrhythmias (➡ Ventricular tachyarrhythmia post-MI, p. 40) and cardiopulmonary resuscitation (➡ Adult advanced life support, p. 6–7).
- *Aortic dissection* (➡ Aortic dissection: assessment, p. 148–9).
- *History of prolonged cocaine use* accelerates the process of atherosclerosis.

Ventricular tachyarrhythmia post-MI

Accelerated idioventricular rhythm

- Common (up to 20%) in patients with early reperfusion in first 48h.
- Usually self-limiting and short-lasting, with no haemodynamic effects.
- If symptomatic, accelerating sinus rate with atrial pacing or atropine may be of value. Suppressive antiarrhythmic therapy (lidocaine, amiodarone) is only recommended with degeneration into malignant ventricular tachyarrhythmias.

Ventricular premature beats (VPB)

- Common and not related to incidence of sustained VT/VF.
- Generally treated conservatively. Aim to correct acid–base balance and electrolyte abnormalities (aim $K^+ > 4.0\text{mmol/L}$ and $Mg^{2+} > 1.0\text{mmol/L}$).
- Peri-infarction β -blockade reduces VPB.

Non-sustained and monomorphic VT

- Associated with a worse clinical outcome.
- Correct reversible features such as electrolyte abnormalities and acid–base balance (aim $K^+ > 4.5\text{mmol/L}$ and $Mg^{2+} > 1.0\text{mmol/L}$).
- DC cardioversion for haemodynamic instability.
- Non-sustained VT and haemodynamically stable VT (slow HR $< 100\text{bpm}$) can be treated with amiodarone (300mg bolus IV over 30min, followed by 1.2g infusion over 24h). Lidocaine is no longer recommended as first line. Procainamide is an effective alternative but is arrhythmogenic.
- For VT despite amiodarone, consider overdrive pacing.

Ventricular fibrillation and polymorphic VT

- A medical emergency and requires immediate defibrillation.
- In refractory VF, consider vasopressin 40U IV bolus.
- Amiodarone 300mg IV bolus to be continued as an infusion (see previous section) if output restored.
- Manage as cardiac arrest with usual ALS protocol (➡ Adult advanced life support, pp. 6–7).

Atrial tachyarrhythmia post-MI

- Includes SVT, AF, and atrial flutter.
- If the patient is haemodynamically unstable, they must undergo immediate synchronized DC cardioversion (press the ‘synch’ button on the defibrillator).
- Haemodynamically stable patients can be treated with digoxin, β -blockers, and/or calcium channel blockers (see Table 1.8).
- Amiodarone can be used to restore sinus rhythm. However, it is not very effective in controlling rate. Class I agents should generally be avoided, as they increase mortality.
- In AF and atrial flutter, patients should undergo anticoagulation to reduce embolic complications if there are no contraindications.

Bradyarrhythmias and indications for pacing

Alternating or isolated RBBB/LBBB do not need pacing, unless haemodynamically unstable or progression to higher levels of block. New bifascicular block [RBBB with either left axis deviation (LAD) or right axis deviation (RAD)] or bundle branch block with first-degree AV block may require prophylactic pacing, depending on the clinical picture. Indications for pacing should not delay reperfusion therapy. Venous access (femoral or internal jugular vein) should be obtained first, and pacing wire inserted later. External temporary cardiac pacing, atropine (300 micrograms to 3mg IV bolus), and isoprenaline can be used to buy time.

Bradyarrhythmias post-MI

First-degree AV block

- Common and no treatment required.
- Significant PR prolongation (>0.20 s) is a contraindication to β -blockade.

Second-degree AV block

- This indicates a large infarction affecting the conducting systems, and mortality is generally $\uparrow$ in this group of patients.
 - Mobitz type I is self-limiting, with no symptoms. Generally, requires no specific treatment. If symptomatic or progression to complete heart block (CHB), will need temporary pacing.
 - Mobitz type II, 2:1, 3:1 should be treated with temporary pacing, regardless of whether it progresses to CHB.

Third-degree AV block

- In the context of an *inferior* MI, can be transient and does not require temporary pacing, unless there is haemodynamic instability or an escape rhythm of <40 bpm.
- Temporary pacing is required with *anterior* MI and unstable inferior MI.

Hypotension and shock post-MI

(See ➡ Cardiac shock, pp. 44–5.)

The important principles in managing hypotensive patients with MI are:

- If the patient is well perfused peripherally, no pharmacological intervention is required. Consider lying the patient flat, with the legs elevated if necessary, provided there is no pulmonary oedema.
- Try to correct any arrhythmia, hypoxia, or acidosis.
- Arrange for an urgent Echo to exclude a mechanical cause for hypotension (e.g. MR, VSD, ventricular aneurysm) that may require urgent surgery.

Patients may be divided into two subgroups

Hypotension with pulmonary oedema

(Also see ➡ Pulmonary oedema: assessment, pp. 92–3.)

- Secure central venous access: internal jugular lines are preferable if the patient may have received thrombolytic therapy.
- Commence *inotropes* (➡ Cardiac shock, pp. 44–5).
- Further invasive haemodynamic monitoring, as available (PA pressures and wedge pressure monitoring, arterial line).
- Ensure optimal filling pressures, guided by physical signs and PA diastolic or wedge pressure. Significant MR will produce large v waves on the wedge trace and give spuriously high estimates of left ventricular end-diastolic pressure (LVEDP).
- Ensure rapid coronary reperfusion (if not already done), either with primary PCI or thrombolysis, depending on availability.
- Intra-aortic balloon counterpulsation (➡ Intra-aortic balloon counterpulsation 1, p. 822) may allow stabilization until PCI can be performed.

Hypotension without pulmonary oedema

This may be due to either RV infarction or hypovolaemia.

Diagnosis

- Check the JVP and RA pressure. This will be low in hypovolaemia and high in RV infarction.
- RV infarction on ECG is seen in the setting of inferior MI and ST elevation in right-sided chest leads (V3R–V4R).

Management

- In either case, cardiac output will be improved by cautious plasma expansion. Give 100–200mL of colloid over 10min and reassess.
- Repeat once if there is some improvement in BP and the patient has not developed pulmonary oedema.
- Invasive haemodynamic monitoring with a PA catheter (Swan–Ganz) is helpful to ensure hypotension is not due to low left-sided filling pressures. Aim to keep PCWP of 12–15mmHg.
- Start inotropes if BP remains low despite adequate filling pressures.
- Use IV nitrates and diuretics with caution, as venodilatation will compromise RV and LV filling and exacerbate hypotension.

See ➡ Right ventricular infarction, p. 28 for management of RV infarction.

Cardiogenic shock

- Affects between 5 and 20% of patients, and up to 15% of MI patients can present with cardiogenic shock.
- Management involves a complex interaction between many medical, surgical, and intensive care teams. with multiple invasive and non-invasive measures. Despite significant advances, prognosis remains poor. Therefore, the absolute wishes of the patient with regard to such an invasive strategy should be respected from the outset.

Diagnosis

A combination of clinical and physiological measures:

- *Clinical*: marked, persistent (>30min) hypotension with SBP <80–90mmHg.
- *Physiological*: low cardiac index (<1.8L/mm/m²), with elevated LV filling pressure (PCWP >18mmHg).

Management

- Complex and must be quick.
- Correct reversible factors, including:
 - Arrhythmias and aim to restore sinus rhythm.
 - Acid–base balance, electrolyte abnormalities.
 - Ventilation abnormalities: intubate if necessary.
- Rapid haemodynamic, echocardiographic, and angiographic evaluation:
 - Haemodynamic: to ensure adequate monitoring and access, including central venous lines, Swan–Ganz, arterial line insertion, urinary catheter.
 - Echocardiographic: to assess ventricular systolic function and exclude mechanical lesions, which may need to be dealt with by emergency cardiac surgery, including MR (NB Tall v waves on PCWP trace), VSD, and ventricular aneurysm/pseudoaneurysm.
 - Angiographic: with a view to PCI or CABG if appropriate.
- Aim to improve haemodynamic status, achieving SBP ≥90mmHg, guided by physical signs and LV filling pressures. As a general guide:
 - PCWP <15mmHg: cautious IV fluids (colloids) in 100–200mL aliquots.
 - PCWP >15mmHg: inotropic support with diuretics (if pulmonary oedema).
- Inotropes should be avoided, if at all possible, in acutely ischaemic patients. The aim should be to rapidly restore/maximize coronary flow and offload the LV. Early revascularization is vital and has been shown to decrease mortality. IABP will partially help achieve improved coronary perfusion, reduce LVEDP, and improve BP, although has not been shown to improve survival in randomized trials.
- If haemodynamic status does not improve post-revascularization and IABP insertion, inotropes should be used. Choice of agent can be difficult and should partly be guided by local protocols and expertise. Generally accepted choices depend on the clinical picture and include:
 - If patient is hypotensive (with pulmonary oedema): start with dopamine (up to 5 micrograms/kg/min), and if ineffective, substitute with adrenaline and/or noradrenaline (NA).

- If patient has adequate BP (with pulmonary oedema): dobutamine to increase CO (starting at 2.5–5 micrograms/kg/min and increasing to 10 micrograms/kg/min), titrating to HR and haemodynamics. Phosphodiesterase inhibitors (PDEs) can be used as an alternative. If hypotension and tachycardia complicate dobutamine/PDE inhibitor treatment, (nor)adrenaline can be added as a 2nd agent to achieve desired haemodynamic effect.
- Use of diuretics, thrombolysis, GP IIb/IIIa antagonists, and LMWH/UFH should follow normal principles and be based on the clinical picture.

Non-ST-elevation acute coronary syndromes (NSTEMI-ACS)

NSTEMI-ACS are closely related conditions with similar clinical presentation, treatment, and pathogenesis, but of varying severity. If there is biochemical evidence of myocardial damage, the condition is termed NSTEMI, and in the absence of damage UA.

The diagnosis of NSTEMI-ACS may not be definitive on presentation and evolves over subsequent hours to days. Therefore, management of patients with NSTEMI-ACS is a progression through a number of risk stratification processes, dependent on history, clinical features, and investigative results, which, in turn, determine the choice and timing of a number of medical and/or invasive treatment strategies (see Fig. 1.8).

Clinical presentation

There are three distinct presentations:

- Rest angina—angina when the patient is at rest.
- New-onset severe angina.
- Increasing angina—previously diagnosed angina which has become more frequent, longer in duration, or lower in threshold.

General examination (as indicated for all ACS; ➡ Acute coronary syndrome, pp. 10–11) must be undertaken, in particular to rule out pulmonary oedema and assess haemodynamic stability, cardiac valve abnormalities, and diaphoresis.

Integrated management plan

We recommend that all patients follow a local integrated care pathway on presentation. The various stages are broadly outlined here. See relevant pages for further information.

- *Initial stabilization* (see also ➡ Acute coronary syndrome, pp. 10–11):
 - Transfer the patient to an area with continuous ECG monitoring and defibrillator facility.
 - Strict bed rest.
 - Give O₂, aspirin 300mg PO, SL nitrate, and mild sedation if required.
 - If pain persists, give diamorphine 2.5–5mg IV PRN, with metoclopramide 10mg IV.
- *General investigations*: similar to STEMI patients (➡ ST-elevation myocardial infarction (STEMI), pp. 12–13; ➡ STEMI: diagnosis 1, p. 14; ➡ STEMI: diagnosis 2, p. 16), including blood for FBC, biochemical profile and markers of myocardial injury, and lipid profile, as well as CRP and thyroid function test (TFT) (if persistent tachycardia). Arrange portable CXR (rule out LVF and mediastinal abnormalities).
- *Confirm diagnosis* (➡ NSTEMI/UA: diagnosis, p. 48).
- *Risk stratification* (➡ NSTEMI/UA: risk stratification, p. 50) in order to determine appropriate medical and invasive treatment strategies. High-risk patients should be admitted to the CCU, and low/intermediate-risk patients to monitored beds in step-down unit.

- *Treatment is based on the patient's risk and includes:*
 - Medical strategies:
 - Anti-ischæmic (➡ NSTEMI/UA: medical management 1, p. 53).
 - Antiplatelet (➡ NSTEMI/UA: medical management 2, pp. 54–5).
 - Antithrombic (➡ NSTEMI/UA: medical management 2, pp. 54–5).
 - Invasive strategies (➡ NSTEMI/UA: invasive versus non-invasive strategies, p. 56).
- *Secondary prevention and discharge.*

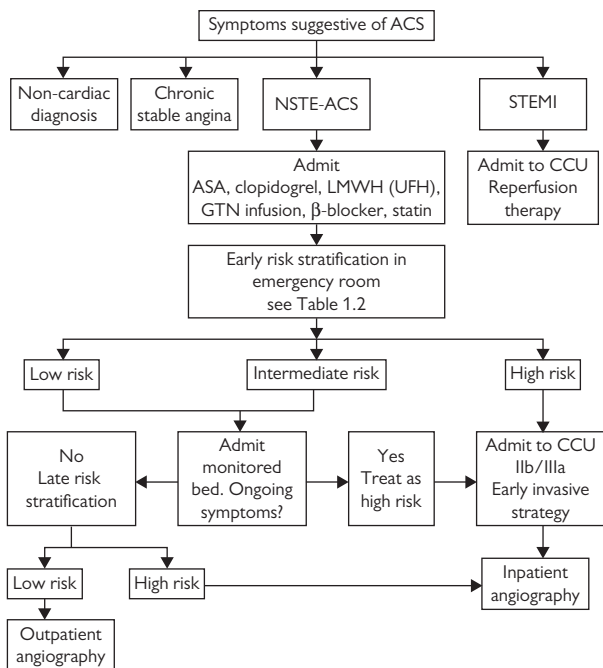


Fig. 1.8 NSTE-ACS—integrated care pathway.

NSTE-ACS: diagnosis

Diagnosis in NSTE-ACS is an evolving process and may not be clear on presentation. A combination of history, serial changes in ECG, and serial changes in biochemical markers of myocardial injury determines the diagnosis. Once a patient has been designated a diagnosis of ACS with probable/possible NSTE-ACS, they will require the following.

Serial ECGs

Changes can be transient and/or fixed, especially if a diagnosis of NSTEMI is made. See Table 1.1 for localization of infarcts from ECG changes.

- ST-segment depression of $\geq 0.05\text{mV}$ is highly specific of myocardial ischaemia (unless isolated in V1–V3 suggesting a posterior STEMI).
- T-wave inversion is sensitive, but non-specific, for acute ischaemia, unless very deep ($\geq 0.3\text{mV}$).
- Rarely Q waves may evolve or there may be transient/new LBBB.

Serial biochemical markers of cardiac injury

These are used to differentiate between NSTEMI and UA, as well as to determine prognosis. We recommend levels at 6, 12, 24, and 48h after the last episode of pain. A positive biochemical marker (CK, CK-MB, or troponin) in the context of one or more of the aforementioned ECG changes is diagnostic of NSTEMI. If serial markers over a 24- to 72-h period from the last episode of chest pain remain negative, UA is diagnosed.

- Cardiac TnT and TnI: are both highly cardiac-specific and sensitive, can detect 'microinfarction' in the presence of normal CK-MB, are not affected by skeletal muscle injury, and convey prognostic information (worse prognosis if positive). Troponins can be raised in non-atherosclerotic myocardial damage (cardiomyopathy, myocarditis, pericarditis) and should therefore be interpreted in the context of the clinical picture. Both TnT and TnI rise within 3h of infarction. TnT may persist up to 10–14 days, and TnI up to 7–10 days. Results must be interpreted with caution in patients with chronic renal failure (CRF). See Fig. 1.5.
- CK levels do not always reach the diagnostic twice the upper limit of normal and generally have little value in diagnosis of NSTEMI.
- CK-MB has low sensitivity and specificity; CK-MB isoforms improve sensitivity (CK-MB2 $>1\text{U/L}$ or CK-MB2:CK-MB1 ratio >1.5), but isoform assays are not widely available clinically.
- Myoglobin is non-cardiac-specific, but levels can be detected as early as 2h after onset of symptoms. A negative test is useful in ruling out myocardial necrosis.

Continuous ECG monitoring

Can detect episodes of silent ischaemia and arrhythmia. Both have been shown to be more prolonged in NSTEMI than in UA.

NSTE-ACS: risk stratification

NSTE-ACS are a heterogeneous group of conditions with variable outcomes. An assessment of risk for adverse outcome is vital to ensure formation of an adequate management plan.

Risk stratification should begin on initial evaluation and continue throughout the hospital stay. At each stage, patients with a high chance of a poor outcome should be identified and managed appropriately.

We recommend at least two formal risk stratification processes.

Early risk stratification

(See Table 1.2.) This should take place on presentation and forms part of the initial assessment used to make a diagnosis. It involves a combination of clinical features, ECG changes, and biochemical markers of cardiac injury, as demonstrated in Table 1.2. Patients are divided into high risk and intermediate/low risk.

- *High-risk* patients should be admitted to the CCU, follow an early invasive strategy, and be managed with a combination of:
 - Acetyl salicylic acid (ASA), clopidogrel/ticagrelor, LMWH, IIb/IIIa inhibitor.
 - Anti-ischaemic therapy (first-line β -blocker, GTN).
 - Early invasive strategy (inpatient catheterization and PCI within 48h of admission).
- *Intermediate/low-risk* patients should be admitted to a monitored bed on a step-down unit and undergo a 2nd inpatient risk stratification once their symptoms have settled, to determine the timing of invasive investigations. Initial management should include:
 - ASA, clopidogrel/ticagrelor, LMWH.
 - Anti-ischaemic therapy (first-line β -blocker, GTN).
 - Undergoing late risk stratification in 48–72h from admission.

Late risk stratification

(See ➡ STEMI: reperfusion therapy (thrombolysis) 1, pp. 22–3.) This involves a number of non-invasive tests to determine the optimal timing for invasive investigations in intermediate/low-risk patients. Suggested guidelines are summarized under ➡ NSTE-ACS: late risk stratification, p. 52. It is generally performed if there have been no further episodes of pain/ischaemia at 24–48h after admission.

- *Intermediate/low-risk* patients who develop recurrent pain and/or ischaemic ECG changes at any point during their admission, heart failure, or haemodynamic instability in the absence of a non-cardiac cause should be managed as high-risk patients (early invasive strategy $\pm$ IIb/IIIa inhibitor).
- Fig. 1.8 is a summary of a recommended integrated care pathway combining diagnosis, risk stratification, and treatment.
- There are other risk stratification assessment scores, including Braunwald and TIMI. As recommended earlier, high-risk patients from these assessments should also follow an early invasive strategy, and intermediate/low-risk patients a more conservative strategy.

Table 1.2 Short-term risk of death from non-fatal MI in patients with UA*

Feature	High risk (at least one of the following features must be present)	Intermediate risk (no high-risk feature but must have one of the following features)	Low risk (no high- or intermediate-risk feature but may have any of the following features)
History	Accelerating tempo of ischaemic symptoms in preceding 48h	Prior MI, peripheral or cerebrovascular disease, or CABG, prior aspirin use	
Character of pain	Prolonged ongoing (>20min) rest pain	Prolonged (>20min) rest angina, now resolved, with moderate or high likelihood of CAD Rest angina (<20min) or relieved with rest or SL GTN	New-onset or progressive CCS Class III or IV angina the past 2 weeks without prolonged (>20min) rest pain but with moderate or high likelihood of CAD
Clinical findings	Pulmonary oedema, most likely due to ischaemia New or worsening MR murmur S3 or new/worsening rales Hypotension, bradycardia, tachycardia Age >75 years	Age >70 years	
ECG	Angina at rest with transient ST-segment changes >0.05mV Bundle branch block, new or presumed new Sustained ventricular tachycardia	T-wave inversion >0.2mV Pathological Q waves	Normal or unchanged ECG during an episode of chest discomfort
Cardiac markers	Elevated (e.g. TnT or TnI >0.1ng/mL)	Slightly elevated (e.g. TnT >0.01 but <0.1ng/mL)	Normal

* Reproduced from Anderson JL, et al. 'ACC/AHA 2007 Guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction'. *J Am Coll Cardiol*, 50:1-157, copyright 2007 with permission from Wolters Kluwer Health, Inc. <http://circ.ahajournals.org/content/116/7/e148>.

NSTE-ACS: late risk stratification

The highest risk of adverse outcome in patients who are designated as intermediate/low risk on presentation is during the early phase of admission. Therefore, it is important that the 2nd risk stratification process occurs within 24–48h of admission if the patient is stable.

Late risk stratification is based on non-invasive investigations. Computed tomography (CT) coronary angiography provides anatomic information and is a useful rule-out in lower-risk patients. Stress testing with dobutamine echocardiography or radionuclide imaging provides functional information. Exercise testing is still used, although the sensitivity and specificity are lower, compared to other non-invasive stress tests.

A patient is regarded as being at high risk of adverse outcome if they fulfil one of the features listed here. These patients should have inpatient cardiac catheterization.

CT coronary angiography

- Requires a HR of ~ 60 or below and sinus rhythm for diagnostic imaging.
- Directly images coronary arteries; however, no functional information.
- Soft plaques may be underestimated.
- Excellent test in low-risk patients to rule out CAD.

Stress radionuclide myocardial perfusion imaging

- Abnormal tracer distribution in >1 territory.
- Cardiac enlargement.

LV imaging

- *Stress echocardiography:*
 - Rest EF $<35\%$.
 - Wall motion score index >1 .
- *Stress radionuclide ventriculography:*
 - Rest EF $<35\%$.
 - Fall in EF $>10\%$.

Exercise ECG test

- *Horizontal/downsloping ST depression with:*
 - Onset at HR <120 bpm or <6.5 metabolic equivalents (METs).
 - Magnitude of >2.0 mm.
 - Post-exercise duration of changes >6 min.
 - Depression in multiple leads, reflecting multi-vessel disease.
- *Abnormal SBP response:*
 - Sustained decrease of >10 mmHg or flat BP response with abnormal ECG.
- *Other:*
 - Exercise-induced ST-segment elevation.
 - VT.
 - Prolonged elevation of HR.

NSTE-ACS: medical management 1

Anti-ischaemic therapy

All patients should be treated with a combination of the listed agents to ensure adequate symptom control and a favourable haemodynamic status (SBP $\approx$ 100–110mmHg, PR 860). All patients should be treated with adequate analgesia, IV nitrates, β -blockers, and statins (if no contraindications). Other agents can also be added, depending on the clinical picture.

- **Analgesia:** diamorphine 2.5–5mg IV (with metoclopramide 10mg IV). Acts as anxiolytic. Reduces pain and SBP through venodilatation and reduction in sympathetic arteriolar constriction. Can result in hypotension (responsive to volume therapy) and respiratory depression (reversal with naloxone 400 micrograms–2mg IV).
- **Nitrates:** GTN infusion (50mg in 50mL of normal saline at 1–10mL/h), titrated to pain and keeping SBP $>$ 100mmHg. Tolerance to continuous infusion develops within 24h, and the lowest efficacious dose should be used. Common side effects are headache and hypotension, both of which are reversible on withdrawal of medication. Absolute contraindication is use of sildenafil in the previous 24h. This can result in exaggerated and prolonged hypotension.
- **β -blockers:** should be started on presentation, unless contraindicated. Initially use a short-acting agent (e.g. metoprolol 12.5–100mg PO tds), which, if tolerated, may be converted to a longer-acting agent (e.g. atenolol 25–1000mg od). Rapid β -blockade may be achieved using short-acting IV agents such as metoprolol (⊖ Beta-blockers, p. 751). Aim for HR of $\sim$ 50–60bpm. Mild LVF is not an absolute contraindication to β -blocker therapy. Pulmonary congestion may be due to ischaemic LV systolic dysfunction and/or reduced compliance. If there is overt heart failure, β -blockade is contraindicated and a calcium antagonist (amlodipine 5–10mg od) can be used. By reducing HR and BP, β -blockers reduce myocardial O_2 demand, and thus angina. When either used alone or in combination with nitrates and/or calcium antagonists, β -blockers are effective in reducing the frequency and duration of both symptomatic and silent ischaemic episodes.
- **Calcium antagonists:** diltiazem 60–360mg PO, verapamil 40–120mg PO tds. Their use aims to reduce HR and BP and is a useful adjunct to treatment with analgesia/nitrates/ β -blockers. Amlodipine/felodipine 5–10mg PO od can be used with pulmonary oedema and in poor LV function. Calcium antagonists alone do not appear to reduce mortality or risk of MI in patients with UA. However, when combined with nitrates and/or β -blockers, they are effective in reducing symptomatic and silent ischaemic episodes, non-fatal MI, and the need for revascularization.
- **Statins (HMG-CoA reductase inhibitors):** high-dose statins (atorvastatin 80mg od) have been shown to reduce mortality and recurrent MI in the acute setting. The role of statins in primary and secondary prevention of future cardiovascular events is well documented.
- **ACEIs:** unlike patients with STEMI in whom early introduction of an ACEI has significant prognostic benefits, specific trials in the NSTE-ACS setting are lacking. However, there is good evidence that both patients with low and high risk of cardiovascular disease will benefit from long-term ACE inhibition (HOPE and EUROPA trials).

NSTE-ACS: medical management 2

Antiplatelet therapy

All patients should be given aspirin and clopidogrel/ticagrelor (unless contraindicated). IIb/IIIa antagonists for high-risk patients only.

- *Aspirin* (300mg PO): should be administered immediately in the emergency department and continued indefinitely (unless contraindicated). It has been shown to consistently reduce mortality and recurrent ischaemic events in many trials. In patients with aspirin hypersensitivity or major gastrointestinal (GI) intolerance, clopidogrel 75mg od should be used.
- *Thienopyridines*: clopidogrel (300mg) or ticagrelor (180mg) should be given on admission to all patients with proven NSTEMI-ACS, regardless of risk, and be continued [75mg od clopidogrel, 90mg twice daily (bd) ticagrelor] for at least 12 months. The PLATO trial showed a decrease in recurrent MI and stroke with ticagrelor, compared to clopidogrel; however, there was a greater incidence of fatal intracranial bleeding. Clopidogrel/ticagrelor should be withheld in patients requiring CABG for 5–7 days to reduce haemorrhagic complications.
- *GP IIb/IIIa antagonists*: there are multiple short- and long-acting commercially available molecules. These agents may be used in conjunction with aspirin, clopidogrel/ticagrelor, and LMWH (or UFH). Eptifibatide and tirofiban should be used in high-risk patients with ongoing ischaemia and elevated troponin, in whom an early invasive management strategy is not planned/available (<24h). In patients with an early invasive strategy, all IIb/IIIa antagonists can be used. Infusion is generally continued for 12h post-PCI. Taken as a group, these agents protect NSTEMI-ACS patients from death and non-fatal MI during the acute phase of their presentation and 24h post-intervention. See Box 1.9 for doses and administration regimen.

Antithrombotic therapy

All patients should be given an LMWH.

- *LMWHs*: have been shown to be as good as, or superior to, UFH in short-term reduction of death, MI, and revascularization in patients with NSTEMI-ACS. They should be used in conjunction with aspirin and clopidogrel in all patients on presentation and be continued for 2–5 days after the last episode of pain and ischaemic ECG changes. Other advantages over UFH include SC administration, lack of monitoring, and reduced resistance and thrombocytopenia. Box 1.9 lists the doses of various agents in use for treating NSTEMI-ACS.
- *UFH*: multiple trials have demonstrated a reduction in the risk of death and MI in patients with UA/NSTEMI. UFH should be started on presentation, as an alternative to LMWH, in conjunction with aspirin and clopidogrel. Infusion should be continued for 2–5 days subsequent to the last episode of pain and/or ischaemic ECG changes. An initial bolus of 60–70U/kg (maximum 5000U) should be followed by an infusion of 12–15U/kg/h ($\approx$ 1000U/h). The infusion rate should be altered to achieve an APTT value of 1.5–2.0 times control. Coagulation should be checked initially every 6h, followed by once every 24h after two consistent values have been obtained.

Thrombolysis

There is no evidence to suggest that combining thrombolytic agents with aspirin, LMWH, and conventional anti-ischaemic therapy is of benefit. In the TIMI IIIB trial, the rtPA group had a worse outcome at 6 weeks and the risk of bleeding was also greater in the thrombolysis group.

For management key points for NSTEMI, see Box 1.10.

Box 1.9 Doses of LMWH and GP IIb/IIIa antagonists for treating NSTEMI-ACS

LMWH

- Dalteparin: 120U/kg bd (max. 10 000U bd).
- Enoxaparin: 1mg/kg bd (100U/kg bd).
- Fondaparinux: 2.5mg od.

GP IIa/IIIa antagonists

- Abciximab: bolus 250 micrograms/kg over 1min, followed by IV infusion 125ng/kg/min.
- Tirofiban: 400ng/kg/min for 30min, followed by IV infusion 100ng/kg/min.
- Eptifibatide: bolus 180 micrograms/kg, followed by IV infusion 2 micrograms/kg/min.

Box 1.10 Management key points: NSTEMI

- Continuous ECG monitoring.
- O₂.
- Analgesia: diamorphine (+ metoclopramide), GTN (monitor BP).
- Aspirin, clopidogrel/ticagrelor, LMWH.
- β -blockers: initially short-acting agent, e.g. metoprolol (if no contraindications).
- High-dose statins.
- GP IIb/IIIa antagonists for high-risk patients only.
- Referral to cardiac rehabilitation on discharge.

NSTE-ACS: invasive versus non-invasive strategies

Current evidence supports early angiography and revascularization in patients who present with either high-risk features or intermediate/low-risk features with ongoing symptoms. Furthermore, low- and intermediate-risk patients who settle on medical therapy should undergo symptom-limited, non-invasive stress testing to identify the cohort of patients with an ↑ risk of adverse outcome. This 2nd group will also benefit from early invasive management.

Patients managed with an early conservative strategy tend to have an ↑ need for antianginal therapy and rehospitalization for angina, and many undergo coronary angiography within the year.

The following groups are recommended to benefit from an early invasive strategy (inpatient cardiac catheterization and PCI):

- Patients with high-risk features of NSTEMI-ACS:
 - Recurrent angina/ischaemic ECG changes despite optimal medical therapy.
 - Elevated troponin.
 - New/presumed new ST-segment depression.
 - Chest pain with clinical features of heart failure (pulmonary oedema, new/worsening MR, S3 gallop).
 - Haemodynamic instability.
 - Sustained VT.
- Poor LV systolic function (EF <40%).
- Patients allocated to low/medium risk, in whom subsequent non-invasive testing demonstrates high-risk features.
- PCI in previous 6 months.
- Previous CABG.
- Patients with other comorbidities (e.g. malignancy, liver failure, renal disease), in whom risks of revascularization are not likely to outweigh benefits.

NSTE-ACS: discharge and secondary prevention

- *Length of hospital stay*: will be determined by symptoms and the rate of progression through the NSTE-ACS pathway. Generally patients are hospitalized for 3–7 days.
- *Secondary prevention*: remains of paramount importance and is similar in principle to STEMI patients (➔ STEMI: predischARGE risk stratification, pp. 30–1).

Arrhythmias: general approach

Both tachyarrhythmias and bradyarrhythmias may present with significant symptoms and haemodynamic compromise. The approach to patients with arrhythmias depends upon:

- The effects of the rhythm on the patient.
- The diagnosis from the ECG and the rhythm.
- Any underlying cardiac abnormality or identifiable precipitant (see Box 1.11).

Effects of the rhythm on the patient

Patients with signs of severe haemodynamic compromise

- Impending cardiac arrest.
- Severe pulmonary oedema.
- Shock: SBP <90mmHg.
- Depressed consciousness.

If the patient is in cardiac arrest, then follow the ALS protocol. If the patient is conscious, but severely compromised, then seek urgent anaesthetic support and urgent synchronized DC cardioversion to manage tachyarrhythmias. For bradyarrhythmias, inotropic support (e.g. isoprenaline), external pacing, or temporary transvenous pacing should be considered (➡ Bradyarrhythmias: general approach, pp. 86–7).

Patients with mild to moderate compromise

- Mild pulmonary oedema.
- Low cardiac output, with cool peripheries and oliguria.
- Angina at rest.

Try to record a 12-lead ECG, if possible, and a long rhythm strip before giving any pharmacological agents and/or defibrillation. This will be invaluable for long-term management. If they deteriorate, treat as for severe haemodynamic compromise.

Diagnosing the arrhythmia

The main distinctions to make are:

- Tachy- (>120/min) versus brady- (<60/min) arrhythmia.
- Narrow (≤ 120 ms or three small squares) versus broad QRS complex.
- Regular versus irregular rhythm.

Box 1.11 Multiple common precipitating factors*Underlying cardiac disease*

- IHD.
- Acute or recent MI.
- Angina.
- MV disease.
- LV aneurysm.
- Congenital heart disease.
- Abnormalities of resting ECG.
- Pre-excitation (short PR interval).
- Long QT (congenital or acquired).

Drugs

- Antiarrhythmics.
- Sympathomimetics (β_2 -agonists, cocaine).
- Antidepressants (tricyclic).
- Adenylate cyclase inhibitors (aminophylline, caffeine).
- Alcohol.

Metabolic abnormalities

- $\downarrow$ or $\uparrow K^+$.
- $\downarrow$ or $\uparrow Ca^{2+}$.
- $\downarrow Mg^{2+}$.
- $\downarrow P_a O_2$.
- $\uparrow P_a CO_2$.
- Acidosis.

Endocrine abnormalities

- Thyrotoxicosis.
- Pheochromocytoma.

Miscellaneous

- Febrile illness.
- Emotional stress.
- Smoking.
- Fatigue.

Tachyarrhythmias heart rate >120bpm

(See Box 1.12.)

History

Previous cardiac disease, palpitations, dizziness, chest pain, symptoms of heart failure, recent medication, and family history, particularly of cardiac conditions or sudden cardiac death. Ask specifically about conditions known to be associated with certain cardiac arrhythmias (e.g. AF: alcohol, thyrotoxicosis, MV disease, IHD, pericarditis; VT: previous MI, LV aneurysm).

Examination

BP, heart sounds and murmurs, signs of heart failure, carotid bruits.

Investigations

If the patient is haemodynamically stable:

- 12-lead ECG and rhythm strip:
 - Regular versus irregular rhythm.
 - Narrow versus broad QRS complex.
- Blood tests:
 - FBC, biochemistry, glucose (urgently).
 - Ca^{2+} , Mg^{2+} (especially if on diuretics).
 - Biochemical markers of myocardial injury.
- Where appropriate:
 - Blood cultures, CRP, erythrocyte sedimentation rate (ESR).
 - TFTs.
 - Drug levels.
 - ABGs.
- CXR:
 - Heart size.
 - Evidence of pulmonary oedema.
 - Other pathology (e.g. Ca bronchus → AF, pericardial effusion → sinus tachycardia, hypotension ± AF).

In haemodynamically unstable patients, some of these investigations might need to be completed after restoration of stable rhythm.

Management

Haemodynamically unstable patients

- Arrhythmias causing severe haemodynamic compromise (cardiac arrest, SBP <90mmHg, severe pulmonary oedema, evidence of cerebral hypoperfusion) require urgent correction, usually with external defibrillation. Drug therapy requires time and haemodynamic stability.
- The only exception is a patient in chronic AF with an uncontrolled ventricular rate—defibrillation is unlikely to cardiovert to sinus rhythm. Rate control and treatment of the precipitant are first line. At the same time, factors that could increase the HR in a previously stable AF patient should be considered, such as infection.

- Sedate awake patients with midazolam (2.5–10mg IV) $\pm$ diamorphine (2.5–5mg IV + metoclopramide 10mg IV) for analgesia. Beware respiratory depression and have an anaesthetist, flumazenil, and naloxone to hand, and always ask for anaesthetic assistance if not experienced in this.
- Formal anaesthesia with propofol is preferred, but remember the patient may not have an empty stomach and precautions should be taken to prevent aspiration (e.g. cricoid pressure, ET intubation).
- Start at 150J biphasic synchronized shock, and increase as required.
- If tachyarrhythmia recurs or is unresponsive, try to correct $\downarrow P_aO_2$, $\uparrow P_aCO_2$, acidosis, or $\downarrow K^+$. Give Mg^{2+} (8mmol IV stat) and shock again. Amiodarone 150–300mg bolus IV may also be used.
- Give specific antiarrhythmic therapy (see Table 1.3).

Haemodynamically stable patients

- Admit and arrange for continuous ECG monitoring and 12-lead ECG.
- Try vagotonic manoeuvres [e.g. Valsalva or carotid sinus massage (CSM)];  Narrow complex tachyarrhythmias (SVT), pp. 72–3].
- If diagnosis is clear, introduce appropriate treatment.
- If there is doubt regarding the diagnosis, give adenosine 6mg as a fast IV bolus, ideally in a big antecubital vein, followed promptly by 5–10mL of saline flush. (Consider starting with a lower dose in patients taking dipyridamole.) If no response, try 9, 12, and 18mg in succession, with continuous ECG rhythm strip.
- Definitive treatment should start as soon as the diagnosis is known ( Treatment options in tachyarrhythmias, p. 62;  Broad complex tachycardia: diagnosis, p. 64;  Monomorphic ventricular tachycardia (MVT), pp. 66–7;  Polymorphic ventricular tachycardia, pp. 68–9;  Ventricular tachycardia: drugs, p. 70;  Narrow complex tachyarrhythmias (SVT), pp. 72–3;  Dosages of selected antiarrhythmics for SVT, p. 75;  Atrial fibrillation: assessment, pp. 76–7;  Atrial fibrillation: management, pp. 78–9;  Atrial fibrillation: rate control, p. 81;  Atrial flutter, p. 82;  Multifocal atrial tachycardia, p. 83;  Accessory pathway tachycardia (AV re-entrant tachycardia), p. 84;  Atrioventricular nodal re-entry tachycardia, p. 85).

Box 1.12 General principles

- *Narrow complex tachycardias* most commonly originate in the atria or AV node (i.e. SVT; see Fig. 1.10).
- *Irregular, narrow complex tachycardia* is most commonly AF or atrial flutter with varying AV block.
- *Broad complex tachyarrhythmias* may originate from either the ventricles (VT) or from the atria or AV node (SVT) with aberrant conduction to the ventricles (RBBB or LBBB configuration).
- If the patient has previous documented arrhythmias, compare the morphology of the current arrhythmia to old ECGs. The diagnosis of VT versus SVT and therapy may be evident from the last admission.
- In a patient with a documented history of CAD, always treat a bundle branch block as VT, unless proven otherwise.

Treatment options in tachyarrhythmias

(See Table 1.3.)

Table 1.3 Treatment options in tachyarrhythmias

Sinus tachycardia	Look for cause; β-blockade if anxious		
Atrial fibrillation	Rate control (AV node)	Cardioversion to sinus rhythm	Prevention
Atrial flutter	● Digoxin	● Flecainide	● Amiodarone
SVT	● β-blockade	● Amiodarone	● Sotalol
➡ Narrow complex tachyarrhythmias (SVT), pp. 72–3)	● Calcium blocker (e.g. verapamil)	● Sotalol	● Quinidine
		● Disopyramide	● Procainamide
		● Synchronized DC shock	
Junctional tachycardias (AVNRT)	● Adenosine	● Digoxin	
➡ Atrioventricular nodal re-entry tachycardia, p. 85)	● β-blockade	● Flecainide	
	● Verapamil	● Synchronized DC shock	
	● (Vagal stimulation)		
Accessory pathway tachycardias (i.e. AVRT)	At AV node	At accessory pathway	Termination only
➡ Accessory pathway tachycardia (AV re-entrant tachycardia), p. 84)	● Adenosine	● Sotalol	● Synchronized DC shock
	● β-blockade	● Flecainide	
		● Disopyramide	
		● Quinidine	
		● Amiodarone	
VT	Termination and prevention		
➡ Ventricular tachycardia: drugs, p. 70)	● Lidocaine	● Flecainide	
	● Procainamide	● Disopyramide	
	● Amiodarone	● Propafenone	
	● Magnesium	● β-blockade	
	● DC shock		

Broad complex tachycardia: diagnosis

(QRS width >120ms or >3 small squares)

Diagnostic approach

The following principles can be used to distinguish between different forms of broad complex tachyarrhythmia.

1. Examine the rhythm strip. Is it regular or irregular?

Regular

- VT (mono-/polymorphic).
- SVT or atrial flutter with bundle branch block.
- Atrial flutter or SVT with pre-excitation (e.g. WPW).

Irregular

- AF, atrial flutter, or multifocal atrial tachycardia with bundle branch block.
- Pre-excited AF (e.g. WPW).
- Torsades de pointes (polymorphic VT).

2. Are there any features on the 12-lead ECG that help distinguish VT from SVT with aberrancy?

Factors favouring SVT

- A grossly irregular broad complex tachycardia with rates ≥ 200 /min suggests AF with conduction over an accessory pathway.
- Slowing or termination by vagotonic manoeuvres.
- Evidence of atrial and ventricular coupling (e.g. with 1:2 AV block).

Factors favouring or diagnostic of VT

- Cycle length stability (<40ms R–R variation).
- QRS >140ms (3.5 small squares), especially with normal duration when compared with previous ECG in sinus rhythm.
- Marked LAD (negative in lead II).
- QRS concordance in chest leads. If the predominant deflection of the QRS is positive, this is highly suggestive of VT.
- In patients with previous LBBB or RBBB, it is difficult to distinguish VT from SVT with aberrancy. A different QRS morphology in tachycardia suggests VT (other clues are given in Table 1.4).
- Fusion or capture beats.
- Independent atrial activity.
- Documented CAD or reduced EF.

3. What are the effects of adenosine?

The transient AV block produces one of three results:

- The s adenosine (and experienced chest tightness with the injection). Higher doses are required in patients on theophyllines. The diagnosis is most likely to be VT.

If there is any doubt about the diagnosis in the acute setting, the patient must be treated as VT, until proven otherwise.

Morphologic rules

For any broad complex tachycardia with 'bundle branch block' morphology, assume it is VT unless features are present, as shown in Table 1.4, which could support the diagnosis of an SVT.

Table 1.4 Differentiating broad complex tachyarrhythmias*

	RBBB	LBBB
Lead V1	rSR' with R' > r RS with R > S	rS or QS with time to S wave nadir <70ms
Lead V6	If a Q wave is present, it must be 40ms and <0.2mV	R wave with no Q wave

Sensitivity 90%; specificity 67–85%.
* Source: data from Griffith MJ, et al. (1994). 'Ventricular tachycardia as default diagnosis in broad complex tachycardia.' *Lancet* 343: 386–8.

Monomorphic ventricular tachycardia (MVT)

Management

(See Box 1.13.)

1. *Assess airway, breathing, and circulation immediately.*
2. *If patient is haemodynamically unstable*
 - If develops VT while monitored, consider precordial thump—this can induce a mechanical premature ventricular complex, interrupting the VT circuit and terminating the arrhythmia. It must not delay external defibrillation.
 - Immediate unsynchronized external defibrillation (200J, 200J, 360J). Patient is often unconscious and if so, no sedation is required.
3. *If patient is haemodynamically stable*
 - Patient should initially be treated with IV pharmacological agents. If this is unsuccessful, they can be electrically cardioverted under sedation/ anaesthesia.
 - Chemical cardioversion is empiric, and the choice of agent depends on local policy and expertise. We recommend IV amiodarone, sotalol, or procainamide as first-line agents. Amiodarone is the agent of choice in the context of poor LV function. Second-line agents include lidocaine and β -blockers (the latter is particularly valuable in the setting of MI/ acute ischaemia).
 - Give IV magnesium (8mmol bolus over 2–5min, followed by 60mmol in 50mL of glucose over 24h) for all patients, especially if there is a risk of hypomagnesaemia (e.g. diuretics, excessive ethanol intake). With recurrent VT, a bolus dose can be repeated safely. Save a serum sample for analysis later.
4. *Correct reversible factors*
 - Ischaemia must be treated, especially in the context of post-infarction VT. This can initially be achieved with β -blockers. Patients should undergo revascularization at the earliest opportunity (➡ STEMI: reperfusion by primary percutaneous coronary intervention, pp. 20–1).
 - Electrolyte abnormalities must be corrected (aim $K^+ \geq 4.0$ –4.5, $Mg^{2+} \geq 1.0$).
 - Acidosis: if severe ($pH \leq 7.1$), give bicarbonate (8.4% sodium bicarbonate 50mL via a central line over 20min).
5. *If there is recurrent or persistent VT*
 - Synchronized DC shock under sedation or anaesthesia, with an anaesthetist present in case of sudden deterioration.
 - Overdrive pacing using a temporary transvenous wire may be used to terminate VT. The combination of prolonged temporary pacing and antiarrhythmics for recurrent VT is particularly effective in situations where the VT is provoked by bradycardia. If possible, rhythm strips of onset of runs of VT must be analysed, looking for bradycardia, heart block, or sick sinus syndrome. Dual-chamber temporary pacing may improve cardiac output by restoring AV synchrony.

6. Maintenance therapy

- Usually oral and depends on the aetiology of VT. Patient must be discussed with the cardiac electrophysiologist early and options for EPS, radiofrequency ablation of VT focus, and/or implantable cardioverter-defibrillator (ICD) implantation explored. Patient will need ambulatory ECG monitor, exercise testing, or more invasive stimulation tests to monitor effectiveness of therapy.

Box 1.13 Key points: monomorphic VT

- Defined as ≥ 3 consecutive ventricular ectopics at a rate $\geq 100/\text{min}$.
- Common early post-MI (up to 40%). If self-limiting, without haemodynamic compromise, does not require treatment.
- Sustained VT in the setting of acute MI (LV dysfunction) is associated with a poor prognosis (short and long term) and requires urgent treatment. Patients should undergo electrophysiological assessment for ICD insertion.
- Accelerated idioventricular rhythm or 'slow VT' (rate 50–100/min) requires treatment if hypotensive (from loss of atrial contribution).

Investigations

- ECG: acute MI, prolonged QT interval.
- CXR: cardiomegaly, pulmonary oedema.
- U&Es: hypokalaemia, renal impairment.
- Mg^{2+} , Ca^{2+} : ? deficiency.
- Cardiac enzymes: small rises common after DC shock.
- ABG: ? hypoxia, acidosis.
- Echo: for LV function and to exclude structural abnormality (e.g. aneurysm).

Once the acute episode is over, consider referral to a cardiologist for:

- Holter monitoring.
- Exercise testing.
- Coronary angiography.
- VT stimulation (provocation) testing.

Polymorphic ventricular tachycardia

General management principles are identical to those for MVT. Most patients will be haemodynamically unstable and must undergo external defibrillation. Polymorphic ventricular tachycardia (PVT) occurring in the following circumstances requires specific therapy:

- Ischaemic PVT in the context of MI.
- Non-ischaemic PVT with QT prolongation (torsades de pointes).
- PVT associated with Brugada syndrome.

Ischaemic PVT

- Occurs in conjunction with acute MI and chronic myocardial ischaemia.
- MVT in the context of MI can convert to PVT.
- Primary treatment is complete revascularization. This must be followed by Holter monitoring, exercise ECG, and electrophysiological evaluation to determine the arrhythmia threshold.
- A subset of patients, especially with poor LV function or where MVT degenerates into PVT, may require ICD implantation.

Non-ischaemic PVT with prolonged QT interval (torsades de pointes)

This is an irregular polymorphic VT (often self-limiting), which appears to 'twist' about the isoelectric line. It occurs in the setting of prolongation of the QT interval ($QTc > 500\text{ms}$) (see Box 1.14), but the relationship between the degree of prolongation and the risk of serious arrhythmias is unpredictable. It may present as recurrent syncope or dizziness. Quite often, patients are mistaken as having seizures.

Brugada syndrome

- Brugada syndrome¹ is characterized by the triad of:
 - ST elevation in V1–V3 (may only be present on provocation test)
 - RBBB.
 - Sudden death (or family history of sudden death) from VF.
- It is common in Japan and in South East Asia. Men are affected more than women.
- The inheritance pattern is autosomal dominant, and some families have a mutation in the cardiac sodium channel SCN5A.
- Must obtain specialist advice from a cardiac electrophysiologist. Patients will require electrophysiological studies, with a view to ICD implantation.
- Diagnosis is made by serial ECGs after administration of flecainide 2mg/kg body weight IV in 10min or procainamide 10mg/kg IV in 10min. The test is positive if an additional 1mm ST elevation appears in leads V1, V2, and V3. All positive individuals should undergo EPS and further specialist evaluation.

Box 1.14 Causes of prolonged QT interval

Acquired

- **Drugs:**
 - *Antiarrhythmics* (quinidine, procainamide, disopyramide, amiodarone, sotalol).
 - *Antipsychotics* (pimozide, thioridazine).
 - *Antihistamines* (terfenadine, astemizole, especially if other prescribed drugs interact with them (e.g. ketoconazole, erythromycin)).
 - *Antimalarials* (especially halofantrine).
 - *Organophosphate poisoning*.
- Electrolyte abnormalities ($\downarrow K^+$, $\downarrow Mg^{2+}$, and $\downarrow Ca^{2+}$).
- Severe bradycardia (CHB or sinus bradycardia).
- Intrinsic heart disease (IHD, myocarditis).
- Intracranial haemorrhage (especially subarachnoid).

Congenital long QT syndromes

- Jervell–Lange–Nielsen syndrome (autosomal recessive, with deafness).
- Romano–Ward syndrome (autosomal dominant, normal hearing).

NB Although amiodarone and sotalol prolong the QT interval, PVT from these drugs is rare.

$$\text{Normal } Q_{tc} = \frac{QT}{\sqrt{(RR \text{ interval})}} = 0.38 - 0.46s \text{ (9–11 small squares)}$$

Management

Congenital long QT

- PVT in congenital QT prolongation is adrenergically driven, and treatment must include long-term β -blockade (e.g. propranolol).
- Other adjunctive treatment includes pacemaker implantation and left stellate ganglionectomy.
- Patients should be considered for ICD therapy. On occasions, decisions may be difficult because of the young age of patients.

Acquired long QT

- The primary principle is to correct QT prolongation.
- Offending agent(s) must be identified and discontinued immediately.
- PVT in acquired QT prolongation is often secondary to prolonged pauses, which must be avoided.
- All patients should receive IV Mg^{2+} (8mmol as a bolus over 2–5min, followed by a 60mmol infusion over 24h).
- Overdrive temporary pacing (either ventricular or atrial) terminates the arrhythmia. Continued pacing prevents recurrence of PVT.
- Isoprenaline may be used, while preparations are being made for pacing. This accelerates the atrial rate and captures the ventricles. Aim for a rate of 110–120bpm.

References

1. <http://www.brugada.org>

Ventricular tachycardia: drugs

(See Table 1.5.)

Table 1.5 Dosages of selected antiarrhythmics for acute treatment of VT

Drug	Loading dose	Maintenance dose
Magnesium sulfate	8mmol (2g) IV over 2–15min (repeat once if necessary)	60mmol/48mL of saline at 2–3mL/h
Lidocaine	100mg IV over 2min (repeat once if necessary)	4mg/min for 30min 2mg/min for 2h 1–2mg/min for 12–24h
Procainamide	100mg IV over 2min. Repeat every 5min to max. of 1g	2–4mg/min IV infusion 250mg every 6h PO
Amiodarone	300mg IV over 60min via central line, followed by 900mg IV over 23h, 200mg PO tds × 1 week, then 200mg PO bd × 1 week	200–400mg od IV or PO
Disopyramide	50mg IV over 5min, repeated up to max. of 150mg IV, 200mg PO	2–5mg/min IV infusion 100–200mg every 6h PO
Flecainide	2mg/kg IV over 10min (max. 150mg)	1.5mg/kg IV over 1h, then 100–250 micrograms/kg/h IV for 24h or 100–200mg PO bd
Bretylium	5–10mg/kg (7500mg) IV over 10–15min	1–2mg/min IV infusion

Narrow complex tachyarrhythmias (SVT)

These originate within the atrium or the conduction system above the bundle of His (see Fig. 1.9). The important distinction to make is between regular and irregular tachyarrhythmias (see Table 1.6). Features of the different arrhythmias are shown in Table 1.7. The diagnosis not to miss is atrioventricular re-entrant tachycardia (AVRT) (tachycardias involving an accessory pathway), as digoxin and verapamil are contraindicated.

Making the diagnosis

This can be done by careful examination of the 12-lead tachycardia ECG rhythm strip and the effect of inducing AV block.

Examination of ECG Important features to demonstrate are whether the rhythm is regular or irregular, and to examine for the presence/absence and morphology of P waves.

Irregular rhythm

- No P waves visible:
 - Irregular rhythm with no discernible P wave (chaotic baseline with *f* waves): treat as AF (➡ Atrial fibrillation: assessment, pp. 76–7).
 - Irregular rhythm with no discernible P wave and 'saw-tooth' flutter waves (especially in inferior leads and V1): treat as *atrial flutter with variable block* (➡ Atrial flutter, p. 82).
- P waves visible:
 - Irregular rhythm with multiple P wave morphologies (>3) and varying PR intervals: treat as multifocal atrial tachycardia (MAT) (➡ Multifocal atrial tachycardia, p. 83).

Regular rhythm

- No P waves visible:
 - No discernible P wave and 'saw-tooth' flutter waves (especially in inferior leads and V1): treat as *atrial flutter with block* (➡ Atrial flutter, p. 82).
- P waves visible:
 - P waves with normal morphology: treat as sinus tachycardia or sinus node re-entry tachycardia.
 - P waves within, or distorting the start or end of, QRS complex: treat as *atrioventricular nodal re-entry tachycardia (AVNRT)* (➡ Atrioventricular nodal re-entry tachycardia, p. 85).
 - QRS complex may/may not be followed by P waves with different morphology to sinus P waves: treat as AVRT (➡ Accessory pathway tachycardia (AV re-entrant tachycardia), p. 84).

Induce AV block By vagotonic manoeuvres (e.g. Valsalva, CSM) and, if unsuccessful, with adenosine. [Adenosine 6mg fast IV bolus (3mg if via central line), followed promptly by 5–10mL of saline flush. If no response, try 9mg, 12mg, and then 18mg.] Check that the patient has received a therapeutic dose of adenosine (and experienced chest tightness with the injection). Higher doses are required in patients on theophyllines, lower in patients on diprydamole.

- AVNRT and AVRT may terminate with adenosine.
- Transient AV block will unmask AF, flutter, and atrial tachycardia, but will not terminate.

- The exact diagnosis may be left to an experienced cardiologist.
- If there is degeneration of the rhythm into broad complex tachyarrhythmia and/or haemodynamic compromise, the patient must be electrically cardioverted immediately.

It is important to remember that SVT with previous bundle branch block/aberrancy or AVRT with pre-excitation can present with broad complex tachycardia. Differentiation from VT may be difficult, and if in doubt, the patient must be treated as VT until proven otherwise. ECG features to distinguish between the two are outlined under  Broad complex tachycardia: diagnosis, p. 64.

Table 1.6 Features of regular versus irregular tachycardia

Regular tachycardia	Irregular tachycardia
• Sinus tachycardia • Atrial flutter (with 2:1 or greater block) • AVRT (i.e. with accessory pathway, e.g. WPW) • AVNRT • Intra-atrial re-entry tachycardia	• AF • Atrial flutter with variable block • MAT

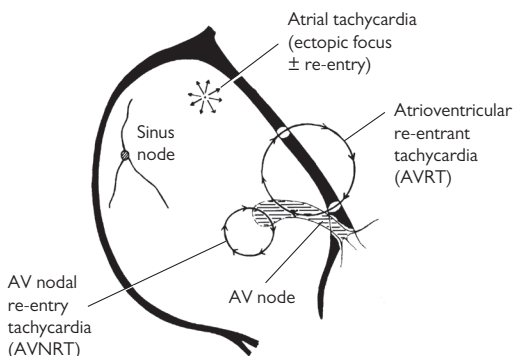


Fig. 1.9 Types of supraventricular tachycardia.

Table 1.7 Differential diagnosis of SVT

Arrhythmia	P wave configuration	Effect of adenosine	Comment
Sinus tachycardia (100–200/min)	Normal P waves	Transient AV block	
Atrial fibrillation (<200/min)	f waves. Chaotic	Transient AV block	Irregular rhythm. Adenosine causes rate to slow briefly. Fast AF with broad QRS seen in AVRT (e.g. WPW)
Atrial flutter (75–175/min)	Flutter waves (saw-tooth) (II, III, aVF, and VI)	Transient AV block	Adenosine may convert to AF
AVNRT (140–200/min)	Inverted buried in QRS (usually not seen)	Terminates	Most common recurrent SVT in adults
AVRT (e.g. WPW or accessory pathway) (150–250/min)	Inverted after QRS (inferior leads, RP > PR interval)	Terminates	Normal QRS if antegrade down AV node; broad QRS if antegrade down pathway
Atrial tachycardia (Intra-atrial re-entry) (100–200/min)	Abnormal P wave (PR < RP), 2:1 AV block may be seen	Transient AV block	Digoxin toxicity, lung disease, organic heart disease
MAT (100–130/min)	Multiple P wave morphologies	Transient AV block	Associated with lung disease and hypoxaemia

NB Any of these may be associated with broad QRS complexes from either a pre-existing bundle branch block or a rate-related intraventricular conduction abnormality.

Dosages of selected antiarrhythmics for SVT

(See Table 1.8.)

Table 1.8 Dosages of selected antiarrhythmics for treatment of SVT

Drug	Loading dose	Maintenance dose
Digoxin	IV 0.5–1mg in 50mL of saline over 1–2h PO 0.5mg every 12h for two doses, then 0.25mg every 12h for 2 days	0.0625–0.25mg od (IV or PO)
Amiodarone	IV 300mg over 60min via central line, followed by 900mg IV over 23h <i>or</i> PO 200mg tds × 1 week, then 200mg PO bd × 1 week <i>or</i> PO 400mg tds for 3 days	200–400mg od (IV or PO)
Drug	Dosage	
Propranolol	IV 1mg over 1min, repeated every 2min up to max. 10mg PO 10–40mg 3–4 times a day	
Atenolol	IV 2–10mg by slow injection PO 25–100mg daily	
Sotalol	IV 20–60mg by slow injection PO 80–160mg bd	
Verapamil	IV 5mg over 2min; repeated every 5min up to max. 20mg PO 40–120mg tds	
Procainamide	IV 100mg over 2min; repeated every 5min up to max. 1g PO 250mg every 6h	
Disopyramide	IV 50mg over 5min; repeated every 5min up to max. 150mg PO 100–200mg every 6h	
Flecainide	IV 2mg/kg over 10min (max. 150mg) <i>or</i> PO 100–200mg bd	
Metoprolol	IV 5mg PO 25–100mg	

Atrial fibrillation: assessment

Presentation

- AF may present with palpitations, chest pain, breathlessness, collapse, or hypotension. Less commonly, it may present with an embolic event (stroke, peripheral embolus) or be asymptomatic. It occurs in 10–15% of patients post-MI.
- Look for signs of an underlying cause (see Box 1.15).
- Try to establish the duration of the AF—this will determine subsequent management (see later sections).

Investigations

These should be directed at looking for a precipitant and underlying heart disease. All patients should have:

- ECG:
 - Broad QRS if aberrant conduction.
 - ST-T-wave changes may be due to rapid rate, digoxin, or underlying cardiac disease.
- CXR: cardiomegaly, pulmonary oedema, intrathoracic precipitant, valve calcification (mitral stenosis).
- U&Es: hypokalaemia, renal impairment.
- Cardiac enzymes: ? MI. Small rise after DC shock.
- Thyroid function: thyrotoxicosis may present as AF only.
- Drug levels: especially if taking digoxin.
- Mg^{2+} , Ca^{2+} .
- ABG: if hypoxic, shocked, or ? acidotic.
- Transthoracic (TTE)/transoesophageal echocardiography (TOE): for LV function and valve lesions and to exclude intracardiac thrombus or particularly thrombus in the LA appendage prior to cardioversion to sinus rhythm.
- Other investigations depend on suspected precipitant.

Immediate management

Stabilize the patient

- General measures (➡ Tachyarrhythmias heart rate >120bpm, pp. 60–1) are as for any patient with an arrhythmia. Obtain venous access. Send bloods (➡ Tachyarrhythmias heart rate >120bpm, pp. 60–1) and, if possible, check K^+ immediately on an ITU machine.
- Correct any electrolyte abnormality.
- If severe acidosis ($pH \leq 7.1$), give 8.4% sodium bicarbonate 50mL slowly IV over 20min.
- CSM or IV adenosine may help confirm the diagnosis, revealing chaotic atrial activity. This is particularly helpful in patients with a rate of 150 bpm where atrial flutter should always be considered. CSM or adenosine will slow the ventricular rate and reveal flutter waves.
- Does the ECG in AF show intermittent or constant delta waves? This suggests WPW, and digoxin and verapamil are contraindicated.

Further management

- Cardiovert to sinus rhythm, if appropriate.
- Control the ventricular response rate.
- Try to prevent further episodes of AF.

Box 1.15 Causes of atrial fibrillation

Underlying cardiac disease

- IHD.
- MV disease.
- Hypertension.
- Heart failure.
- Cardiomyopathy.
- Pericarditis.
- Endocarditis.
- Myocarditis.
- Atrial myxoma.
- Post-cardiac surgery.

Separate intrathoracic pathology

- Pneumonia.
- Malignancy (primary or secondary).
- PE.
- Trauma.

Metabolic disturbance

- Electrolytes ($\downarrow K^+$, $\downarrow Mg^{2+}$).
- Acidosis.
- Thyrotoxicosis.
- Drugs (alcohol, sympathomimetics).

Atrial fibrillation: management

(See Box 1.16.)

Rate control versus cardioversion

- Important principles required to make a decision are:
 - Are there advantages in immediate cardioversion (e.g. ongoing ischaemia with fast ventricular rhythm, pulmonary oedema, ↓ consciousness, haemodynamic instability)?
 - If the patient is cardioverted, will they remain in sinus rhythm (e.g. underlying sepsis/thyroid disease, large LA, poor LV, MV disease)?
 - What are the risks of thromboembolic complications and is anticoagulation required (helpful to calculate the CHADS2 and CHA2D2-Vasc scores)?
- Cardioversion can be achieved chemically or with external defibrillation.

Haemodynamically unstable patients

- All hypotensive patients should undergo external defibrillation using a synchronized shock of initially 150J biphasic DC (⚡ DC cardioversion 1, pp. 818–19).
- Do not attempt to defibrillate hypotensive patients with known chronic AF or a known underlying cause driving a fast ventricular response. Chances of success are very low (e.g. mitral stenosis, severe LV dysfunction, hyperthyroidism, sepsis).
- Relative contraindications to defibrillation need to be weighed against the patient's clinical condition. If possible, aim to optimize the clinical picture before cardioversion:
 - Hypokalaemia may be quickly corrected by giving 20mmol over 1h in 100mL of normal saline via a central line.
 - If digoxin toxicity is a possibility, ensure K^+ is 4.5–5mmol/L and give magnesium sulfate 8mmol in 50mL of normal saline over 15min, before attempting defibrillation at low energies initially (e.g. 20–50J).
 - AF of >48h duration carries a significant risk of thromboembolic complications, unless the patient is on long-term anticoagulation and INR has been therapeutic. Consider performing TOE first.
- The procedure is detailed under ⚡ DC cardioversion 1, pp. 818–19.
- If DC shock fails initially:
 - Give IV amiodarone 300mg over 60min via a central line (followed by IV infusion of 900–1200mg over 24h).
 - Correct hypokalaemia (aim for K^+ 4.5–5.0mmol/L).
 - Attempt further DC shock.

Haemodynamically stable patients

- The initial aim should be rapid pharmacological rate control, followed by a decision regarding restoration of sinus rhythm if appropriate.
- When making a decision regarding restoration of sinus rhythm, current evidence must be taken into account:
 - Management of AF with a rhythm control strategy alone has no survival benefit over a rate control strategy, as long as moderate- and high-risk patients are anticoagulated.

- Rate control is not inferior to rhythm control for prevention of death and cardiovascular morbidity in patients with persistent AF after electrical cardioversion.
- Patients in sinus rhythm are more likely to report a better 'quality of life' than those in AF.

AF >2 days' duration

- Control the ventricular rate using one of, or a combination of, digoxin and class II and IV agents (including: β -blocker, verapamil, diltiazem). Can be given as IV preparation to achieve rapid rate control, followed by oral preparations (see Table 1.8 for doses).
- If patient not anticoagulated, start LMWH/UFH (UFH: give bolus of 5000U, followed by infusion, aiming for an APTT ratio of 2–3) until warfarinization is adequate (aim for an INR of 2–3).
- Sinus rhythm may be restored by class Ia, Ic, and III agents (we recommend amiodarone, sotalol, quinidine, disopyramide, and flecainide).
- If the patient needs to be electrically cardioverted, TOE must be performed to look for intracardiac thrombus or spontaneous contrast (a marker of very sluggish flow). If negative, DC cardioversion may be performed safely. Give a bolus of LMWH/UFH before cardioversion, if not already on LMWH/UFH.
- Discharge when stable. Consider readmission following 4–6 weeks of warfarin for DC cardioversion.

AF <2 days' duration

- Although the risk of embolism in new-onset AF is low, we recommend anticoagulation at presentation with LMWH/UFH and subsequently warfarin (see previous section).
- Attempt chemical cardioversion if there are no contraindications to potential agents. Chances of success are much higher with shorter duration of AF. Possible agents include:
 - Flecainide 2mg/kg IV over 10min (max. dose 150mg). Must be avoided in patients with known IHD and/or poor LV function.
 - Disopyramide 50–100mg IV. Ventricular rate may increase and fibrillatory waves coarsen before reverting to sinus rhythm, so load with digoxin/ β -blocker/verapamil before giving this.
 - Amiodarone may be used IV/PO. Dosing requires a central line, and it may take 24–48h for sinus rhythm to be achieved. Amiodarone has relatively poor rate control properties and may need to be combined with a β -blocker or verapamil initially.
- If cardioversion inappropriate or unsuccessful, achieve rate control as indicated in the previous section.
- DC cardioversion can be attempted if rate control is difficult.
 - Discharge when stable. Anticoagulation may be achieved on an outpatient basis, if appropriate.

Box 1.16 Management key points: AF

All patients: treat reversible causes (e.g. thyrotoxicosis, chest or other infection), and correct hypokalaemia/hypomagnesaemia.

Haemodynamically unstable patients

- DC cardioversion (under general anaesthesia or sedation).

Haemodynamically stable patients

- AF >48h duration:
 - Control ventricular rate (digoxin, β -blockers, verapamil, diltiazem).
 - Consider anticoagulation if moderate/high risk of thromboembolism or contemplating elective DC cardioversion.
- AF <48h duration:
 - Consider 'pill-in-pocket' strategy for cardioversion (flecainide or β -blockers).
 - Chemical (e.g. flecainide or amiodarone) or DC cardioversion.
 - If cardioversion is inappropriate or unsuccessful: rate control.
 - Consider anticoagulation.

Atrial fibrillation: rate control

Controlling the ventricular response rate

- Check that there is no history of WPW and that no delta waves are visible on the ECG.
- We recommend β -blockers and calcium channel blockers (verapamil and diltiazem) as first-line agents for rate control. They both have the advantage of maintaining the ventricular rate during exertion. If a single agent is not adequate: either (1) combine β -blockers and calcium channel blockers (if BP adequate) or (2) add digoxin or amiodarone.
- Digoxin is an alternative drug and can equally be used as a first-line agent. Patients should initially be given a full loading dose. The maintenance dose varies (0.0625–0.25mg od), depending on body mass, renal function, age, etc. Digoxin is poor at controlling the ventricular rate during exertion.
- In patients with poor LV function, calcium channel blockers may not be appropriate, inducing heart failure, reflex tachycardia, and hypotension. β -blockers might be appropriate to help both with the heart failure (when not acute) and HR. Digoxin, with or without amiodarone, is a good combination (amiodarone will increase the plasma digoxin level, so halve the maintenance digoxin dose).
- Other drugs that may be tried to control the ventricular rate are listed in Table 1.8.
- If controlling the ventricular rate is difficult, consider alternative diagnosis, in particular MAT. Digoxin may make the arrhythmia worse (➡ Multifocal atrial tachycardia, p. 83).

Long-term management

- Look for causes (see Box 1.15), and arrange an Echo.
- Patients successfully cardioverted acutely should be commenced on a prophylaxis regimen using class Ia, Ic, or III agents (e.g. sotalol, amiodarone, flecainide, propafenone). The choice of agent must be individualized:
 - Lone AF: use class Ic agents first, followed by class III or Ia if it fails.
 - Poor LV function: amiodarone and some β -blockers are the agents of choice.
 - IHD: class III agents and β -blockers (prevent ischaemia and, as a result, ischaemia-driven AF) are agents of choice.
- If subsequently considered to be at low risk, treatment may be stopped at 1 month. Seek cardiac opinion if in doubt.
- Patients cardioverted electively should remain on warfarin and rhythm prophylaxis for 1 month, pending outpatient review. The current trend is to keep patients at moderate or high risk of thromboembolism on anticoagulation life-long, unless there are concerns.
- Patients with paroxysmal AF require long-term therapy to try to maintain sinus rhythm (classes III, Ic, and Ia). Digoxin only controls the ventricular rate and does not prevent AF. These patients may need long-term anticoagulation, depending on:
 - Frequency and length of AF paroxysms
 - Presence of underlying structural or cardiac abnormalities, and
 - Other systemic risk factors of thromboembolic complications.

Atrial flutter

- This is rarely seen in the absence of underlying CAD, valve disease, myocardial disease, pericarditis, PE, or thyrotoxicosis.
- The atrial rate is 280–320/min, and atrial activity is seen as flutter waves in inferior leads and V1 on the ECG.
- The AV node conduction is slower (most commonly 2:1 block, sometimes 3:1 or 4:1), and this determines the ventricular rate.
- Vagotonic manoeuvres and adenosine increase the AV block and reveal the flutter waves but only very rarely terminate the arrhythmia.

Management

- Atrial flutter should be treated in exactly the same way as AF.
- DC cardioversion is the therapy of choice, as flutter can be resistant to pharmacological therapy.
 - Lower energies are needed (50–100J).
 - If flutter has been present >48h, perform TOE and then cardiovert, with LMWH/UFH cover (as for AF).
- Medical management:
 - Pharmacological agents recommended are similar to AF. Rate control and reversion rates can be low.
 - Digoxin, verapamil, and β -blockers can all be used to slow ventricular response. IV preparations can be used for more rapid action. The overall response can be poor. IV verapamil (2.5–5mg over 1–2min, repeated every 5min to a maximum dose of 20mg) will slow the response rate and occasionally restore sinus rhythm in 15–20% of patients.
 - Ibutilide and dofetilide have been reported to have reversion rates of 50% and 70%, respectively. Alternative agents are amiodarone, flecainide, quinidine, and procainamide.
 - NB Class Ia drugs can enhance AV conduction and must always be used after rate control has been achieved.
- Flutter ablation can be performed, particularly in resistant and/or recurrent atrial flutter. Discuss with a cardiac electrophysiologist, as with increasing success of the procedure and reduced risk, this should be considered for all patients with resistant or recurrent flutter.

Multifocal atrial tachycardia

- Commonly occurs in critically ill patients, especially with obstructive airways disease, who may be hypoxaemic and hypercapnic. Theophylline toxicity should be excluded.
- Characterized by at least three different P wave morphologies with varying PP and PR intervals. Atrial nodal rate is 120–180 with 1:1 conduction.
- Rapid regular rhythm may be difficult to differentiate from AF. However, differentiation is very important, as MAT is not responsive to DC cardioversion and is exacerbated by digoxin.

Management

- The only true effective *treatment is to treat the underlying illness*. If associated with lung disease, aim to improve P_aO_2 and P_aCO_2 .
- Electrolyte abnormalities must be corrected. High-dose Mg^{2+} IV may restore sinus rhythm (15g over 5h).
- There is increasing evidence from small trials that metoprolol is the most effective therapy. Use cautiously IV. However, most patients with MAT and COPD may not tolerate even a cardioselective β -blocker.
- Verapamil is an alternative agent (5mg IV over 2min and repeated every 5min up to a maximum of 20mg; then 40–120mg PO tds) if the ventricular rate is consistently over >100/min and the patient is symptomatic.
- DC shock and digoxin are ineffective.

Accessory pathway tachycardia (AV re-entrant tachycardia)

- The three most common accessory pathways that produce paroxysmal tachycardias are described in  Types of accessory pathways, p. 84.
- During re-entry tachycardia, the delta wave is lost, as the accessory pathway is only conducting retrogradely.
- AF may produce very rapid ventricular rates, as the accessory pathway has rapid antegrade conduction (unlike the AV node). The ECG will show the delta wave in some or all of the QRS complexes.

Management

- DC cardioversion should be used early if the tachycardia is poorly tolerated.
- Class Ia, Ic, and II agents are suitable for chemical cardioversion. We recommend IV flecainide or disopyramide. β -blocker may also be given, especially if other agents are contraindicated (see Table 1.8).
- Digoxin and verapamil should be avoided, as they may accelerate conduction down the accessory pathway. Amiodarone is dangerous, unless given very slowly (e.g. 300mg IV over 2–4h).
- If recurrent symptoms, the patient should be referred for electrophysiological assessment and radiofrequency ablation. Seek specialist advice for long-term medical management.

Types of accessory pathways

Kent bundle (Wolff–Parkinson–White syndrome)

- ECG: short PR interval and delta wave:
 - Type A Positive δ wave in V1–V6
Negative in lead I
(Posterior left atrial pathway)
 - Type B Biphasic or negative δ wave in V1–V3
Positive in lead I
(Lateral right atrial pathway)
 - Concealed No δ wave visible, as pathway only conducts retrogradely.
- Associated with Ebstein's, hypertrophic obstructive cardiomyopathy (HOCM), and mitral valve prolapse.

Mahaim pathway (rare)

Pathway connects the AV node to the right bundle, resulting in a tachycardia with LBBB morphology.

James pathway (Lown–Ganong–Levine syndrome) (rare)

- Short PR interval, but no delta wave.
- Pathway connects the atria to the AV node, the bundle of His, or the fascicles.

Atrioventricular nodal re-entry tachycardia

- AVNRT occurs secondary to a micro re-entrant circuit in the AV node.
- General principles are as outlined under  Tachyarrhythmias heart rate >120bpm, pp. 60–1 (HR >120bpm apply).
- Rate control can be achieved with (IV and PO) digoxin, β -blockers, and calcium channel blockers. β -blockers and calcium channel blockers can also promote reversion into sinus rhythm.
- Class Ic and Ia agents (we recommend flecainide) can also be used for chemical cardioversion and maintenance of sinus rhythm long term.
- If arrhythmia is resistant to treatment, consider electrical cardioversion.
- Patients with recurrent symptoms should be referred for electrophysiological assessment and possible radiofrequency ablation.

Bradyarrhythmias: general approach

- Ask specifically about previous cardiac disease, palpitations, blackouts, dizziness, chest pain, symptoms of heart failure, and recent drugs.
- Examine carefully, noting the BP, JVP waveform (? cannon waves), heart sounds and murmurs, and signs of heart failure.

Investigations

- 12-lead ECG and rhythm strip:
 - Look specifically for the relationship between P waves and QRS complex.
 - A long rhythm strip is sometimes necessary to detect CHB if atrial and ventricular rates are similar.
- Blood tests:
 - FBC, biochemistry, glucose (urgently).
 - Ca^{2+} , Mg^{2+} (especially if on diuretics).
 - Biochemical markers of cardiac injury.
- Where appropriate:
 - Blood cultures, CRP, ESR.
 - TFTs.
 - Drug levels.
 - ABGs.
- CXR:
 - Heart size.
 - ? signs of pulmonary oedema.

Management

Haemodynamically unstable patients

- Give O_2 via face mask if the patient is hypoxic on air.
- Keep nil by mouth (NBM) until definitive therapy has been started to reduce the risk of aspiration in case of cardiac arrest or when the patient lies supine for temporary wire insertion.
- Secure peripheral venous access.
- Bradyarrhythmias causing severe *haemodynamic compromise* (cardiac arrest, asystole, SBP <90mmHg, severe pulmonary oedema, evidence of cerebral hypoperfusion) require immediate treatment and temporary pacing (the technique is described under ➡ Indications for temporary pacing, pp. 806–7).
 - Give atropine 1mg IV (Min-I-Jet®) bolus; repeat, if necessary, up to a maximum of 3mg.
 - Give isoprenaline 0.2mg IV (Min-I-Jet®) if there is a delay in pacing and the patient remains unstable. Set up an infusion (1mg in 100mL bag of normal saline, starting at 1mL/min, titrating to HR).
 - Set up an external pacing system (see Box 1.17), if available, and arrange for transfer to a screening room for transvenous pacing. If fluoroscopy is not available, 'blind' transvenous pacing using a balloon-tipped pacing wire may be attempted.
- Bradycardia in shock is a poor prognostic sign. Look for a source of blood loss, and begin aggressive resuscitation with fluids and inotropes.

Haemodynamically stable patients

- Admit to CCU with continuous ECG monitoring.
- Keep atropine drawn up and ready in case of acute deterioration.
- Does the patient require a temporary wire immediately? It may be of value to have appropriate central venous access (femoral or internal jugular vein) in place in case of need for emergency temporary wire insertion.
- Refer the patient to a cardiologist.

Box 1.17 External cardiac pacing

- In emergencies, external cardiac pacing may be used first, but this is painful for the patient and is only a temporary measure until more 'definitive' transvenous pacing wire can be inserted.
- External cardiac pacing is useful as a standby in patients post-MI when the risks of prophylactic transvenous pacing after thrombolysis are high.
- Haemodynamically stable patients with anterior MI and bifascicular block may be managed simply by application of the external pacing electrodes and having the pulse generator ready, if necessary.
- Familiarize yourself with the machine in your hospital when you have some time—a cardiac arrest is not the time to read the manual for the apparatus!

Sinus bradycardia or junctional rhythm

(HR <50 bpm)

Causes

- Young, athletic individual (physiological bradycardia).
- Drugs (β -blockers, morphine).
- Hypothyroidism.
- Hypothermia.
- $\uparrow$ vagal tone:
 - Vasovagal attack.
 - Nausea or vomiting.
 - Carotid sinus hypersensitivity.
 - Acute MI (especially inferior).
- Ischaemia or infarction of the sinus node.
- Chronic degeneration of sinus or AV nodes or atria.
- Cholestatic jaundice.
- Raised intracranial pressure (ICP).

Management

- If hypotensive or pre-syncopal, treat as described under  Bradyarrhythmias: general approach, pp. 86–7:
 - Atropine 600 micrograms–3mg IV bolus, repeating as necessary.
 - Isoprenaline 0.5–10 micrograms/min IV infusion.
 - Temporary pacing.
 - Avoid and take steps to correct precipitants (see  Causes, p. 88).
 - Stop any drugs that may suppress the sinus or AV nodes.
- Long-term treatment:
 - If all possible underlying causes removed and if symptomatic bradycardia remains, refer for permanent pacing.
 - Consider Holter monitoring in patients with possible episodic bradycardia. R–R intervals >2.5s may require permanent pacing, especially if associated with symptoms.

Intraventricular conduction disturbances

Common causes of bundle branch block

- IHD.
- Hypertensive heart disease.
- Valve disease (especially aortic stenosis).
- Conduction system fibrosis (Lev and Len'gre syndromes).
- Myocarditis or endocarditis.
- Cardiomyopathies.
- Cor pulmonale (RBBB) (acute or chronic).
- Trauma or post-cardiac surgery.
- Neuromuscular disorders (myotonic dystrophy).
- Polymyositis.

Management

- General principles (➡ Bradyarrhythmias: general approach, pp. 86–7) apply.
- Interventricular conduction disturbances on their own do not require temporary pacing. However, when associated with haemodynamic disturbance or progression to higher levels of block (even if intermittent), insertion of a transvenous pacing wire must be considered. The need for longer-term pacing is dependent on the persistence of symptoms and underlying cause. Consult a cardiologist. See ➡ Indications for temporary pacing, pp. 806–7 for situations where temporary pacing is indicated.

Types of atrioventricular conduction block

First-degree heart block

- Prolongation of the PR interval ($>0.22s$, >5 small squares).

Second-degree heart block

- *Mobitz type 1 (Wenckebach)*: progressive increase in PR interval, with intermittent complete AV block (P wave not conducted).
- *Mobitz type 2*: the PR interval is constant, but there is intermittent failure to conduct the P wave. Often occurs in the presence of broad QRS complex.
- 2:1, 3:1, etc.: as in Mobitz type 2, the PR interval is constant, but every second (in 2:1) or third (in 3:1) P wave is not conducted on a regular basis.

Third-degree (complete) heart block

Complete AV dissociation. If the P and QRS rates are similar, a long rhythm strip or exercise (to speed up the atrial rate) will help demonstrate dissociation.

Causes

- Associated with acute infarction or ischaemia.
- Drugs (β -blockers, digitalis, calcium channel blockers).
- Conduction system fibrosis (Lev and Len'gre syndromes).
- $\uparrow$ vagal tone.
- Trauma or following cardiac surgery.
- Hypothyroidism (rarely thyrotoxicosis).
- Hypothermia.
- Hyperkalaemia.
- Hypoxia.
- Valvular disease (aortic stenosis, incompetence, endocarditis).
- Myocarditis (diphtheria, rheumatic fever, viral, Chagas' disease).
- Associated with neuromuscular disease, i.e. myotonic dystrophy.
- Collagen vascular disease [systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma].
- Cardiomyopathies (haemochromatosis, amyloidosis).
- Granulomatous disease (sarcoid).
- Congenital heart block.
- Congenital heart disease [atrial septal defect (ASD), Ebstein's, patent ductus arteriosus (PDA)].

Management

- Principles are listed under  Bradyarrhythmias: general approach, pp. 86–7.
- In summary, all symptomatic patients must have pacing (temporary or permanent). The higher the level of block (irrespective of symptoms), the greater the progression to CHB and/or chances of asystole.
- See  Indications for temporary pacing, pp. 806–7 for situations when temporary pacing is indicated. Some cardiologists may prefer to implant a permanent system straightaway.

Pulmonary oedema: assessment

Presentation

- Acute breathlessness, cough, frothy bloodstained (pink) sputum.
- Collapse, cardiac arrest, or shock.
- Associated features may reflect underlying cause:
 - Chest pain or palpitations: ? IHD/MI, arrhythmia.
 - Preceding history of dyspnoea on exertion: ? IHD, poor LV.
 - Oliguria, haematuria: ? acute renal failure (ARF) (⚡ Acute kidney injury 1, pp. 290–2).
 - Seizures, signs of intracranial bleed.

Causes

A diagnosis of pulmonary oedema or 'heart failure' is not adequate. An underlying cause must be sought in order to direct treatment appropriately. These may be divided into:

- ↑ pulmonary capillary pressure (hydrostatic).
- ↑ pulmonary capillary permeability.
- ↑ intravascular oncotic pressure.

Often a combination of factors are involved (e.g. pneumonia, hypoxia, cardiac ischaemia) (see Box 1.19).

The main differential diagnosis is acute (infective) exacerbation of COPD (previous history, quiet breath sounds, wheeze, fewer crackles). It may be difficult to differentiate the two clinically, and indeed sometimes they could coexist.

Principles of management

1. Stabilize the patient—relieve distress and begin definitive treatment.
2. Look for an underlying cause.
3. Address haemodynamic and respiratory issues.
4. Optimize and introduce long-term therapy.

Initial rapid assessment

- If the patient is very unwell (e.g. unable to speak, hypoxic, SBP <100mmHg), introduce stabilizing measures and begin treatment immediately before detailed examination and investigations (see Box 1.18).
- If the patient is stable and/or if there is doubt as to the diagnosis, give O₂ and diuretic, but await the outcome of clinical examination and CXR before deciding on definitive treatment.

Urgent investigations for all patients

- ECG: sinus tachycardia most common. ? any cardiac arrhythmia (AF, SVT, VT). ? evidence of acute ST change (STEMI, NSTEMI, UA). ? evidence of underlying heart disease [left ventricular hypertrophy (LVH), p mitrale].
- CXR: to confirm the diagnosis, look for interstitial shadowing, enlarged hila, prominent upper lobe vessels, pleural effusion, and Kerley B lines. Cardiomegaly may or may not be present. Also exclude pneumothorax, PE (oligaemic lung fields), and consolidation.

- ABG: typically $\downarrow P_aO_2$. P_aCO_2 levels may be $\downarrow$ (hyperventilation) or $\uparrow$, depending on the severity of pulmonary oedema. Pulse oximetry may be inaccurate if peripherally shut down.
- U&Es: ? pre-existing renal impairment. Regular K^+ measurements (once on IV diuretics).
- FBC: ? anaemia or leucocytosis indicating the precipitant.
- Echo: as soon as practical to assess LV function, valve abnormalities, VSD, or pericardial effusion.

Box 1.18 Investigations for patients with pulmonary oedema

All patients should have

- FBC, U&Es, CRP.
- Serial biochemical markers of myocardial injury (troponins, CK, CK-MB).
- LFTs, albumin, total protein.
- ECG.
- CXR.
- ABG.
- TTE ($\pm$ TOE).

Where appropriate consider

- Septic screen (sputum, urine, blood cultures).
- Holter monitor (? arrhythmias).
- Coronary angiography (? IHD).
- Right and left heart catheter (if Echo unable to provide adequate information on pressures, shunts, valve disease).
- Endomyocardial biopsy (myocarditis, infiltration).
- Multigated acquisition (MUGA) scan or cardiac magnetic resonance (CMR), if available.
- Cardiopulmonary exercise test with an assessment of peak O_2 consumption.

Pulmonary oedema: causes

Look for an underlying cause for pulmonary oedema (see Box 1.19).

Box 1.19 Causes of pulmonary oedema

Increased pulmonary capillary pressure (hydrostatic)

- ↑ LA pressure:
 - MV disease.
 - Arrhythmia (e.g. AF) with pre-existing MV disease.
 - Left atrial myxoma.
- ↑ LVEDP:
 - Ischaemia.
 - Arrhythmia.
 - Aortic valve disease.
 - Cardiomyopathy.
 - Uncontrolled hypertension.
 - Pericardial constriction.
 - Fluid overload.
 - High output states (anaemia, thyrotoxicosis, Paget's bone disease, arteriovenous (AV) fistula, beriberi).
 - Renovascular disease.
- ↑ pulmonary venous pressure:
 - L → R shunt (e.g. VSD).
 - Venocclusive disease.
- Neurogenic:
 - Intracranial haemorrhage.
 - Cerebral oedema.
 - Post-ictal.

Increased pulmonary capillary permeability

- Acute lung injury:
 - Acute respiratory distress syndrome (ARDS) (☞ STEMI: thrombolysis 2, p. 24).
- ↓ intravascular oncotic pressure.

Decreased intravascular oncotic pressure

- Hypoalbuminaemia:
 - ↑ losses (e.g. nephrotic syndrome, liver failure).
 - ↓ production (e.g. sepsis).
 - Dilution (e.g. crystalloid transfusion).

NB Critical LA pressure for hydrostatic oedema = serum albumin (g/L) × 0.57.

Pulmonary oedema: management 1

Stabilize the patient

- Patients with acute pulmonary oedema should initially be continuously monitored and managed where full resuscitation facilities are available.
- Sit the patient up in bed.
- Give 60–100% O₂ by face mask (unless contraindicated—COPD).
- If the patient is severely distressed, summon the 'on-call' anaesthetist and inform ITU. If dyspnoea cannot be significantly improved by acute measures (see following text), the patient may require CPAP or mechanical ventilation.
- Treat any haemodynamically unstable arrhythmia—urgent synchronized DC shock may be required.
- Give:
 - Diamorphine 2.5–5mg IV (caution abnormal ABGs).
 - Metoclopramide 10mg IV.
 - Furosemide 40–120mg slow IV injection.
- Secure venous access, and send blood for urgent U&Es, FBC, and cardiac enzymes (including troponin).
- Unless thrombolysis is indicated, take ABG.
- If SBP is ≥90mmHg and the patient does not have aortic stenosis:
 - Give SL GTN spray (two puffs).
 - Start IV GTN infusion 1–10mg/h; increase the infusion rate every 15–20min, titrating against BP (aiming to keep SBP ~100mmHg).
- If SBP is <90mmHg, treat the patient as cardiogenic shock (➡ Cardiogenic shock, pp. 44–5).
- Insert a urinary catheter to monitor urine output, if appropriate.
- Repeat ABG and K⁺ if the clinical condition deteriorates/fails to improve, or after 2h if there is improvement and the original sample was abnormal (serial K⁺ monitoring could also be performed from venous blood).
- Monitor pulse, BP, RR, O₂ saturation with a pulse oximeter (if an accurate reading can be obtained), and urine output.

Further management

Subsequent management of the patient is aimed at ensuring adequate ventilation/gas exchange, ensuring haemodynamic stability, and correcting any reversible precipitants of acute pulmonary oedema.

- Assess the patient's respiratory function:
 - Does the patient require respiratory support? (➡ Respiratory failure: assessment, pp. 198–9)
- Assess the patient's haemodynamic status:
 - Is the patient in shock? (➡ Non-VF/VT (asystole and PEA), pp. 8–9)
- Look for an underlying cause (➡ Pulmonary oedema: causes, p. 94)
- Conditions that require specific treatment:
 - Acute AR and MR (➡ Acute mitral regurgitation, pp. 120–1).
 - Diastolic LV dysfunction (➡ Hypotension and shock post-MI, p. 42).
 - Fluid overload (➡ Pulmonary oedema: specific conditions, p. 100).
 - Renal failure (➡ Acute kidney injury 2, pp. 294–5).
 - Severe anaemia.
 - Hypoproteinaemia (➡ Pulmonary oedema: specific conditions, p. 100).
 - Sepsis (➡ Sepsis syndrome and septic shock, pp. 336–7).

Pulmonary oedema: management 2

If the patient remains unstable and/or deteriorates, take the following steps.

Assess the patient's respiratory function

- Wheeze may be caused by interstitial pulmonary oedema. If there is a history of asthma, give nebulized salbutamol (2.5–5mg), nebulized ipratropium bromide (500 micrograms), and hydrocortisone (200mg) IV. Consider commencing an aminophylline infusion. This will relieve bronchospasm, as well as 'offload' by systemic vasodilatation (➡ Acute severe asthma: immediate therapy, p. 186). However, it may worsen tachycardia, and it can be arrhythmogenic and lower potassium levels (K^+) (supplement to ensure K^+ levels are 4–5mmol/L).
- Indications for further respiratory support include:
 - Patient exhaustion or continuing severe breathlessness.
 - Persistent $P_aO_2 < 8kPa$.
 - Rising P_aCO_2 .
 - Persistent or worsening acidosis ($pH < 7.2$).
- CPAP: this may be tried for cooperative patients, who can protect their airway, have adequate respiratory muscle strength, and are not hypotensive. The positive pressure reduces venous return to the heart and may compromise BP.
- ET intubation and mechanical ventilation may be required, and some positive end-expiratory pressure (PEEP) should be used (➡ Positive end-expiratory pressure, p. 831).
- Discuss the patient with the on-call anaesthetist or ITU team EARLY.

Assess the patient's haemodynamic status

It is important to distinguish between cardiogenic and non-cardiogenic pulmonary oedema, as further treatment is different between the two groups. This may be difficult clinically. A PA (Swan–Ganz) catheter can be considered in experienced centres if the patient's condition will allow.

- Non-cardiogenic pulmonary oedema occurs when the hydrostatic pressure within the capillary system overcomes the plasma oncotic pressure. In patients with hypoalbuminaemia, this will occur at PCWP $< 15mmHg$. The critical PCWP may be estimated by serum albumin (g/L) $\times 0.57$. Thus, a patient with a serum albumin of 15g/L will develop hydrostatic pulmonary oedema at an LA pressure of 8mmHg; a serum albumin of 30g/L will require an LA pressure of $> 17mmHg$, etc.
- Cardiogenic pulmonary oedema is often associated with significant systemic hypotension or low output states. Contributing factors include conditions where there is 'mechanical' impairment to forward flow [e.g. valvular heart disease (especially if acute), VSD] or severe myocardial disease (large MI, myocarditis, cardiomyopathy).
- The gradient between PA diastolic pressure and PCWP (PAD–PCWP) is generally $< 5mmHg$ in cardiogenic, and $> 5mmHg$ in non-cardiogenic, pulmonary oedema (e.g. ARDS).
- The pulse and BP are most commonly elevated due to circulating catecholamines and overactivity of the renin–angiotensin system. Examination reveals sweating, cool and 'shut-down' peripheries, and high pulse volume (assess the carotid or femoral pulses).

Management

(See Box 1.20.)

The general approach involves combination of diuretics, vasodilators, and inotropes. Patients may be divided into two groups:

- Patients in shock (with SBP <100mmHg) (➡ Pulmonary oedema: management 3, pp. 98–9).
- Haemodynamically stable patients with SBP >100mmHg (➡ Pulmonary oedema: management 3, pp. 98–9).

Box 1.20 Management key points: pulmonary oedema

- Sit the patient up in bed.
- O₂.
- IV diamorphine (+ metoclopramide).
- IV furosemide.
- IV GTN infusion (titrate according to BP).
- Look for and treat underlying cause (e.g. ischaemia, arrhythmia, sepsis).
- Consider CPAP or mechanical ventilation if dyspnoea is not improved by acute measures.

Pulmonary oedema: management 3

Patients with SBP <100mmHg

- The patient is in incipient (or overt) shock. The most common aetiology is cardiogenic shock, but remember non-cardiogenic causes (e.g. ARDS, septic shock; ➡ Shock, pp. 328–9).
- Optimal monitoring and access: central line $\pm$ PA catheter (Swan–Ganz), urinary catheter, arterial line (monitoring BP and ABGs). Internal jugular lines are preferable, as the risk of pneumothorax is lower.
- Ensure the patient is not underfilled, using PCWP as a guide (<10mmHg) (mistaken diagnosis, e.g. septic shock from bilateral pneumonia).
- Is there a mechanical cause that may require emergency surgery?
 - Arrange an urgent Echo to rule out:
 - VSD and acute MR in all patients with recent MI with/without new murmur (➡ STEMI: complications, pp. 32–3).
 - Prosthetic heart valve dysfunction (e.g. dehiscence, infection) or pre-existing native aortic or mitral disease that may require surgery.
- Discuss the patient early on with a cardiologist/cardiac surgeon.

The choice of inotropic agent depends on the clinical condition of the patient and, to some extent, the underlying diagnosis.

- Treatment of septic shock is discussed elsewhere (➡ Sepsis syndrome and septic shock, pp. 336–7).
- SBP 80–100mmHg and cool peripheries: start dobutamine infusion at 5 micrograms/kg/min, increasing by 2.5 micrograms/kg/min every 10–15min to a maximum of 20 micrograms/kg/min until BP >100mmHg. This may be combined with dopamine (2.5–5 micrograms/kg/min). However, tachycardia and/or hypotension secondary to peripheral vasodilatation may limit its effectiveness. PDIs (enoximone or milrinone) should be considered where dobutamine fails.
- SBP <80mmHg: give a slow IV bolus of adrenaline (2–5mL of 1 in 1000 solution Min-I-Jet®), and repeat if necessary.
 - Dopamine at doses of >2.5 micrograms/kg/min has a pressor action, in addition to direct and indirect inotropic effects, and may be used at higher doses (10–20 micrograms/kg/min) if the BP remains low. However, it tends to raise the pulmonary capillary filling pressure further and should be combined with vasodilators (e.g. nitroprusside or hydralazine) once the BP is restored (➡ Hypertensive emergencies: drug treatment, pp. 142–3). Beware of arrhythmias at these doses.
 - Adrenaline infusion may be preferred to high-dose dopamine as an alternative inotrope. Once the BP is restored (>100mmHg), vasodilators, such as nitroprusside/hydralazine or GTN infusion, should be added to counteract the pressor effects. Adrenaline can be combined with dobutamine and/or a PDI, especially in the context of a poor ventricle.
- Intra-aortic balloon counterpulsation should also be used with/without inotropes in the context of a potentially reversible cause for pulmonary oedema and shock (e.g. ongoing myocardial ischaemia, VSD, acute MR) (➡ Ventricular septal defect post-myocardial infarction (MI), pp. 34–5).
- Further doses of diuretic may be given.

Patients with SBP ≥ 100 mmHg

- Further doses of diuretic may be given—furosemide 40–80mg IV every 3–4h or as an infusion (e.g. 160–240mg over 24h).
- Continue the GTN infusion, increasing the infusion rate every 15–20min up to 10mg/h, titrating against the BP (aiming to keep SBP ~ 100 mmHg).
- ACEIs can be used if BP is adequate and there are no other known contraindications (e.g. renal artery stenosis, renal failure), although most clinicians will wait after the acute heart failure has settled, as ACEIs might decrease diuresis in this context. Arteriolar vasodilators (nitroprusside or hydralazine) may also be added to, or used instead of, GTN in patients with adequate BP. Arterial pressure should be monitored continuously via an arterial line to prevent inadvertent hypotension.

Long-term management

- Unless a contraindication exists, start an ACEI, increasing the dose to as near the recommended maximal dose as possible. In the context of LV impairment, ACEIs have significant prognostic benefit.
- If ACEIs are contraindicated or not tolerated, consider the use of hydralazine and a long-acting oral nitrate in combination.
- For all patients with impaired EF and New York Heart Association (NYHA) classes III/IV, consider the addition of spironolactone (25–50mg). (NB Monitor renal function and serum potassium.)
- In the context of stable patients (no clinical features of failure) and poor LV function, β -blockers have significant mortality and some symptomatic benefit (NB Start at a very small dose, and increase gradually every 2 weeks, with regular monitoring). Bisoprolol, carvedilol, and metoprolol slow-release (not available in the UK) can all be used.
- Ensure all arrhythmias are treated (➡ Tachyarrhythmias heart rate >120 bpm, pp. 60–1).
- Digoxin can be used for symptomatic improvement.
- Consider multi-site pacing (biventricular) in the context of severe LV dysfunction, broad QRS complex, or Echo evidence of dyssynchrony.
- Patients with AF or poor LV function should be considered for long-term anticoagulation.
- Patients <60 years with severe irreversible LV dysfunction and debilitating symptoms must be considered for cardiac transplantation and other LV support devices such as left ventricular assist devices (LVADs) as bridge to destination therapy.

Pulmonary oedema: specific conditions

Diastolic LV dysfunction

- This typically occurs in elderly hypertensive patients with LVH where there is impaired relaxation of the ventricle in diastole. There is marked hypertension, pulmonary oedema, and normal or only mild systolic LV impairment.
- With tachycardia, diastolic filling time shortens. As the ventricle is 'stiff' in diastole, LA pressure is $\uparrow$ and pulmonary oedema occurs (exacerbated by AF, as filling by atrial systole is lost).
- Treatment involves control of hypertension with IV nitrates (and/or nitroprusside), calcium blockers (verapamil or nifedipine), and even selective β -blockers (e.g. carvedilol).

Fluid overload

- Standard measures are usually effective.
- In extreme circumstances, venesection may be necessary.
- Check the patient is not anaemic [haemoglobin (Hb) $\geq 10\text{g/dL}$]. Remove 500mL of blood via a cannula in a large vein, and repeat if necessary.
- If anaemic (e.g. renal failure) and acutely unwell, consider dialysis (➡ Acute kidney injury 1, pp. 290–2).

Known (or unknown) renal failure

- Unless the patient is permanently anuric, large doses of IV furosemide may be required (up to 1g, given at 4mg/min), in addition to standard treatment.
- If such treatment fails, or the patient is known to be anuric, dialysis will be required.
- In patients not known to have renal failure, an underlying cause should be sought (see Box 4.2).

Anaemia

- Cardiac failure may be worsened or precipitated by the presence of significant anaemia. Symptoms may be improved in the long term by correcting this anaemia.
- Generally, transfusion is unnecessary with Hb $>9\text{g/dL}$, unless there is a risk of an acute bleed. Treatment of pulmonary oedema will result in haemoconcentration and a 'rise' in Hb.
- If anaemia is thought to be exacerbating pulmonary oedema, ensure that adequate diuresis is obtained prior to transfusion. Give slow transfusion (3–4h per unit) of packed cells, with IV furosemide 20–40mg before each unit.

Hypoproteinaemia

- The critical LA pressure at which hydrostatic pulmonary oedema occurs is influenced by the serum albumin and approximates to [serum albumin concentration (g/L) $\times 0.57$].
- Treatment involves diuretics, cautious albumin replacement, spironolactone (if there is secondary hyperaldosteronism), and importantly treatment of the underlying cause for hypoproteinaemia.

Infective endocarditis (IE)

Clinical presentation of IE is highly variable and dependent on a combination of intracardiac pathology, evolution of the infection, and possible extracardiac involvement. Presentation can be insidious, as in streptococcal infections, with striking constitutional symptoms, such as with *Staphylococcus aureus*.

Presenting features can include the following:

- *Symptoms and signs of the infection:* these include malaise, anorexia, weight loss, fever, rigors, and night sweats. Long-standing infection produces anaemia, clubbing, and splenomegaly.
- *Cardiac manifestations of the infection:* congestive cardiac failure (CCF), palpitations, tachycardia, new murmur, pericarditis, or AV block.
- *Symptoms and signs due to immune complex deposition:*
 - Skin: petechiae (most common), splinter haemorrhages, Osler's nodes [small tender nodules (pulp infarcts) on hands and feet, which persist for hours to days], Janeway lesions (non-tender, erythematous, and/or haemorrhagic areas on the palms and soles).
 - Eye: Roth spots (oval retinal haemorrhages with a pale centre, located near the optic disc), conjunctival splinter haemorrhages, retinal flame haemorrhages.
 - Renal: microscopic haematuria, glomerulonephritis, and renal impairment.
 - Cerebral: toxic encephalopathy.
 - Musculoskeletal: arthralgia or arthritis.

Complications of the infection

- *Local effects:*
 - Valve destruction results in a new or changing murmur. This may result in progressive heart failure and pulmonary oedema.
 - A new harsh pan-systolic murmur and acute deterioration may be due to perforation of the interventricular septum or rupture of the sinus of Valsalva aneurysm into the RV.
 - High-degree AV block (2–4% of IE) occurs with intracardiac extension of the infection into the interventricular septum (e.g. from aortic valve endocarditis).
 - Intracardiac abscess may be seen with any valve infection (25–50% of aortic endocarditis, 1–5% of mitral, but rarely with tricuspid) and is most common in prosthetic valve endocarditis (PVE).
- *Embolic events:*
 - Septic emboli are seen in 20–45% of patients and may involve any circulation (brain, limbs, coronary, kidney, or spleen); PEs with tricuspid endocarditis.
 - Forty to 45% of patients who have had an embolic event will have another.
 - The risk depends on the organism (most common with Gram negative infections, *S. aureus*, or *Candida*) (see Box 1.22) and the presence and size of vegetations (emboli in 30% of patients with no vegetation on Echo, 40% with vegetations of <5mm, and 65% with vegetations of >5mm).

Ask specifically for a history of dental work, infections, surgery, IV drug use, or instrumentation, which may have led to bacteraemia. Examine for any potential sources of infection, especially teeth or skin lesions. Risk factors for endocarditis are shown in Box 1.21.

Box 1.21 Risk factors for IE

High risk

- Prosthetic valves.
- Previous bacterial endocarditis.
- Aortic valve disease.
- MR or mixed mitral disease.
- Cyanotic congenital heart disease.
- PDA.
- Uncorrected left-to-right shunt.
- Intracardiac and systemic–pulmonary shunts.

Moderate risk

- Mitral valve prolapse (MVP) with regurgitation or valve thickening.
- Isolated mitral stenosis.
- Tricuspid valve disease.
- Pulmonary stenosis.
- Hypertrophic cardiomyopathy.
- Bicuspid aortic valve disease.
- Degenerative valve disease in the elderly.
- Mural thrombus (e.g. post-infarction).

Low risk

- MVP without regurgitation.
- Tricuspid regurgitation without structural valve abnormality.
- Isolated ASD.
- Surgically corrected left-to-right shunt, with no residual shunt.
- Calcification of MV annulus.
- IHD and/or previous CABG.
- Permanent pacemaker.
- Atrial myxoma.

Other predisposing factors

- Arterial prostheses or AV fistulae.
- Recurrent bacteraemia (e.g. IV drug users, severe periodontal disease, colon carcinoma).
- Conditions predisposing to infections (e.g. diabetes, renal failure, alcoholism, immunosuppression).
- Recent central line.

In many cases, no obvious risk factor is identified.

IE: diagnosis

Clinical features can be non-specific, and diagnosis difficult. A high index of suspicion must be maintained if patients present with unexplained fever, a predisposing cardiac lesion, bacteraemia, and an embolic phenomenon.

The Duke classification has been devised to help with the diagnosis:

- **Definite endocarditis:** two major criteria, or one major and three minor criteria, or five minor criteria.
- **Possible endocarditis:** findings which fall short of definite endocarditis but are not rejected.
- **Rejected diagnosis:** firm alternative diagnosis, or sustained resolution of clinical features with <4 days of antibiotic therapy.

Major criteria

Positive blood culture

- Typical microorganism for IE from two separate blood cultures.
- Persistently positive blood culture.

Evidence of endocardial involvement

- Positive echocardiogram:
 - Oscillating intracardiac mass (vegetation).
 - Abscess.
 - New partial dehiscence of prosthetic valve.
 - New valve regurgitation.

Minor criteria

- Predisposing condition or drug use.
- Fever $>38^{\circ}\text{C}$.
- Vascular phenomena: arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial and conjunctival haemorrhage, Janeway lesions.
- Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor.
- Microbiological evidence: positive blood cultures, but not meeting major criteria, or serological evidence of organism consistent with IE.
- Echo: positive for IE, but not meeting major criteria.

For common organisms in IE, see Box 1.22.

Box 1.22 Common organisms in IE

- 50–60% Streptococci (especially *Streptococcus viridans* group)
- 10% Enterococci
- 25% Staphylococci:
 - Staphylococcus aureus* = coagulase +ve
 - Staphylococcus epidermidis* = coagulase –ve
- 5–10% Culture – ve
- <1% Gram-negative bacilli
- <1% Multiple organisms
- <1% Diphtheroids
- <1% Fungi

IE: investigations

- *Blood cultures* Take 3–4 sets of cultures from different sites at least an hour apart, and inoculate a minimum of 10mL/bottle for the optimal pick-up rate. Both aerobic and anaerobic bottles must be used. Lab should be advised that IE is a possibility, especially if unusual organisms are suspected. In stable patients on antibiotic therapy, doses must be delayed to allow culture on successive days. Ask for prolonged (fungal) cultures in IV drug users.
- *FBC* May show normochromic, normocytic anaemia (exclude haematinic deficiency), fragmented red blood cells (RBCs), and low haptoglobins, with mechanical valves, neutrophil leucocytosis, and perhaps thrombocytopenia.
- *U&Es* May be deranged (this should be monitored throughout treatment).
- *LFTs* May be deranged, especially with an increase in alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT). Raised LDH if there is RBC fragmentation.
- *ESR/CRP* Acute phase reaction.
- *Urinalysis* Microscopic haematuria $\pm$ proteinuria.
- *Immunology* Polyclonal elevation in serum immunoglobulins (Igs), complement levels.
- *ECG* May have changes associated with any underlying cause. There may be AV block or conduction defects (especially aortic root abscess) and rarely (embolic) acute MI.
- *CXR* May be normal. Look for pulmonary oedema or multiple infected or infarcted areas from septic emboli (tricuspid endocarditis) and to exclude chest cause for sepsis.
- *Echo* TTE may confirm the presence of valve lesions and/or demonstrate vegetations if >2mm in size. TOE is more sensitive for aortic root and mitral leaflet involvement. A normal Echo does not exclude the diagnosis.
- *MRI* Useful in investigation of paravalvular extension, aortic root aneurysm, and fistulae.
- *Dentition* All patients should have an orthopentamograph (OPG)—a panoramic dental X-ray, and a dental opinion.
- *Swabs* Any potential sites of infection (skin lesions).
- *V/Q scan* In cases where right-sided endocarditis is suspected, this may show multiple mismatched defects.
- *Save serum for* *Aspergillus* precipitins, *Candida* antibodies (rise in titre), Q fever (*Coxiella burnetti*), complement fixation test, *Chlamydia* complement fixation test, *Brucella* agglutinins, *Legionella* antibodies, *Bartonella* spp.

IE: antibiotics

‘Blind’ treatment for endocarditis

IE is usually a clinical diagnosis and must be considered in any patient with a typical history, fever, and a murmur with no other explanation. Often antibiotics need to be started before the culture results are available. Be guided by the clinical setting (see Table 1.9); see Box 1.23 for suggested doses.

Table 1.9 Antibiotic treatment of IE*

Presentation	Choice of antibiotic
Gradual onset (weeks)	Benzylpenicillin + gentamicin
Acute onset (days) or history of skin trauma	Flucloxacillin + gentamicin
Recent valve prosthesis [possible meticillin-resistant <i>S. aureus</i> (MRSA), diphtheroid, <i>Klebsiella</i> , <i>Corynebacterium</i> , or nosocomial staphylococci)	Vancomycin (or teicoplanin) + gentamicin + rifampicin
IV drug user	Vancomycin

* Oakley CM; The medical treatment of culture-negative infective endocarditis, *European Heart Journal* 1995; 16 (suppl_B): 90–93, doi:10.1093/eurheartj/16.suppl_B.90. (Translated and) Reprinted by permission of Oxford University Press on behalf of the European Society of Cardiology.

Box 1.23 Suggested antibiotic doses

Benzylpenicillin	4MU (2.4g) q4h IV
Flucloxacillin	2g four times daily (qds) IV
Vancomycin	15mg/kg q12h IV over 60min, guided by levels
Gentamicin	3mg/kg divided in 1–3 doses, guided by levels
Rifampicin	300mg q12h PO
Ciprofloxacin	300mg q12h IV for 1 week, then 750mg q12h PO for 3 weeks

- Identification of an organism is invaluable for further management, and blood cultures should be taken before antibiotics, with meticulous attention to detail.
- Antibiotics should be administered IV, preferably via a tunnelled central (Hickman) line.
- If an organism is isolated, antibiotic therapy may be modified when sensitivities are known.
- Suggested antibiotic combinations are shown in Table 1.9; however, individual units may have specific policies. Patients should be discussed with your local microbiologist.

Duration of treatment

- This is controversial, with a trend towards shorter courses. Microbiology and infectious disease (ID) opinion is important, especially in resistant and/or uncommon organisms. Box 1.24 shows one suggested protocol.
- The duration of treatment varies, depending on the severity of infection and the infecting organism. IV therapy is usually for at least 2 weeks, and total antibiotic therapy is for 4–6 weeks.
- If the patient is well following this period, antibiotic treatment may be stopped. Provided no surgery is indicated (➡ Surgery for IE, pp. 114–15), the patient may be discharged and followed up in outpatient clinic.
- Patients should be advised of the need for endocarditis prophylaxis in the future (see Table 1.10).
- Patients with valvular damage following infection should be followed long term, and patients with VSDs should be considered for closure.

Box 1.24 Suggested treatment protocol

- *Viridans* streptococci and *Streptobovis* (penicillin-sensitive):
 - Benzylpenicillin only (4 weeks).
 - Vancomycin or teicoplanin (4 weeks).
 - Penicillin + aminoglycoside (2 weeks).
 - Ceftriaxone 2g (4 weeks).
- Group B, C, and G streptococci, *S. pyogenes*, *S. pneumoniae*:
 - Penicillin (4 weeks) + aminoglycoside (2 weeks).
 - Vancomycin (4 weeks) + aminoglycoside (2 weeks).
- Group A streptococci:
 - Penicillin (4 weeks).
 - Vancomycin (4 weeks).
- Enterococci:
 - Penicillin + aminoglycoside (4–6 weeks).
 - Vancomycin + aminoglycoside (4–6 weeks).
- Extracardiac infection from septic emboli:
 - Penicillin (4 weeks) + aminoglycoside (2 weeks).
 - Vancomycin (4 weeks) + aminoglycoside (2 weeks).
- *S. aureus* and coagulase-negative staphylococci:
 - Left-sided endocarditis:
 - Flucloxacillin (4–6 weeks) + aminoglycoside (2 weeks).
 - If MRSA: vancomycin + rifampicin (6 weeks) ± aminoglycoside (2 weeks).
 - Right-sided endocarditis:
 - Flucloxacillin (2 weeks) + aminoglycoside (2 weeks).
 - Ciprofloxacin (4 weeks) + rifampicin (3 weeks).
 - If MRSA: vancomycin (4 weeks) + rifampicin (4 weeks).
- Fungi:
 - Amphotericin IV to a total dose of 2.5–3g.

IE: monitoring treatment

Patients need careful clinical monitoring both during and for several months after the infection. Reappearance of features suggestive of IE must be investigated thoroughly to rule out recurrent infection or resistance to the treatment regimen.

Clinical features

- Signs of continued infection, persistent pyrexia, and persistence of systemic symptoms.
- Persistent fever may be due to drug resistance, concomitant infection (central line, urine, chest, septic emboli to lungs or abdomen), or allergy (? eosinophilia, ? leucopenia, ? proteinuria: common with penicillin but may be due to any antibiotic; consider changing or stopping antibiotics for 2–3 days).
- Changes in any cardiac murmurs or signs of cardiac failure.
- Development of any new embolic phenomena.
- Inspect venous access sites daily. Change peripheral cannulae every 3–4 days.

Echo

- Regular (weekly) TTEs may identify clinically silent, but progressive, valve destruction and development of intracardiac abscesses or vegetations.
- The tips of long-standing central lines may develop sterile fibrinous 'fronds', which may be visible on TOE—change the line and send the tip for culture.
- 'Vegetations' need not be due to infection (see Box 1.25).

ECG

Looking specifically for AV block or conduction abnormalities suggesting intracardiac extension of the infection. A daily ECG must be performed.

Microbiology

- Repeated blood cultures (especially if there is continued fever).
- Regular aminoglycoside and vancomycin levels (ensuring the absence of toxic levels and the presence of therapeutic levels). Gentamicin ototoxicity may develop with prolonged use, even in the absence of toxic levels.
- Back titration to ensure that minimum inhibitory and bactericidal concentrations are being achieved.

Laboratory indices

- Regular (daily) urinalysis.
- Regular U&Es and LFTs.
- Regular CRP (ESR every 2 weeks).
- FBC: rising Hb and falling WCC suggests successful treatment; watch for β -lactam-associated neutropenia.
- Serum magnesium (if on gentamicin).

Box 1.25 Causes of 'vegetations' on Echo

- IE.
- Sterile thrombotic vegetations.
- Libman–Sacks endocarditis (SLE).
- Primary antiphospholipid syndrome.
- Marantic endocarditis (adenocarcinoma).
- Myxomatous degeneration of valve (commonly mitral).
- Ruptured mitral chordae.
- Exuberant rheumatic vegetations (black Africans).
- Thrombus ('pannus') on a prosthetic valve.
- A stitch or residual calcium after valve replacement.²

References

2. Michel PL, Acar J (1995). Native cardiac disease predisposing to infective endocarditis. *Eur Heart J* 16(suppl B):2–6.

Culture-negative endocarditis

- The most common reason for persistently negative blood cultures is prior antibiotic therapy, and this affects up to 15% of patients with a diagnosis of IE (see Box 1.26).
- If the clinical response to the antibiotics is good, these should be continued.
- For persisting fever:
 - Withhold antibiotics if not already started.
 - Consider other investigations for a 'pyrexia of unknown origin' (PUO) (➔ Pyrexia of unknown origin, p. 534).
 - If clinical suspicion of IE is high, it warrants further investigation.
 - Repeated physical examination for any new signs.
 - Regular Echo and TOE. 'Vegetations' need not be due to infection (see Box 1.25).
 - Repeated blood cultures, especially when the temperature is raised. Discuss with microbiology about prolonged culturing times (4+ weeks) and special culturing and subculturing techniques. Most HACEK-group organisms can be detected (see Box 1.26).
- Consider unusual causes of endocarditis.
- *Q-fever (Coxiella burnetii)*: complement fixation tests identify antibodies to phase 1 and 2 antigens. Phase 2 antigens are raised in acute illness, and phase 1 antigens in chronic illnesses such as endocarditis. Polymerase chain reaction (PCR) can be performed on operative specimens. Treat with indefinite (life-long) oral doxycycline $\pm$ co-trimoxazole, rifampicin, or quinolone.
- *Chlamydia psittaci*: commonly, there is a history of exposure to birds and there may be an associated atypical pneumonia. Diagnosis is confirmed using complement fixation tests to detect raised antibody titres.
- *Brucellosis*: blood cultures may be positive, although organisms may take up to 8 weeks to grow. Serology usually confirms the diagnosis.
- *Fungi*: *Candida* is the most common species and may be cultured. Detection of antibodies may be helpful, although levels may be raised in normals. Detection of a rising titre is of more use. Other fungal infections (e.g. histoplasmosis, aspergillosis) are rare but may be diagnosed with culture or serology, although these are commonly negative. Antigen assays may be positive, or the organism may be isolated from biopsy material. Fungal IE is more common in patients with prosthetic valves and IV drug users. Bulky vegetations are common. Treatment is with amphotericin $\pm$ flucytosine. Prosthetic valves must be removed. Mortality is >50%.

Box 1.26 Causes of culture-negative endocarditis

- Previous antibiotic therapy.
- Fastidious organism:
 - Nutritionally deficient variants of *Streptococcus viridans*.
 - *Brucella*, *Neisseria*, *Legionella*.
 - *Nocardia*.
 - Mycobacteria.
 - The HACEK* group of oropharyngeal flora.
 - Cell wall-deficient bacteria and anaerobes.
- Cell-dependent organisms.
- Chlamydia, rickettsiae (*Coxiella*).
- Fungi.

* HACEK: *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* spp.

Right-sided endocarditis

- May present as multiple infected PEs (abscesses).
- Always consider this diagnosis in IV drug users (or patients with venous access).
- Endocarditis on endocardial permanent pacemaker leads is a rare, but recognized, cause.
- Patients most commonly have staphylococcal infection and are unwell, requiring immediate treatment and often early surgery.
- Lesions may be sterilized with IV antibiotics.
- Surgery may be required for:
 - Resistant organisms (*S. aureus*, *Pseudomonas*, *Candida*, and infection with multiple organisms).
 - Increasing vegetation size in spite of therapy.
 - Infections on pacemaker leads (surgical removal of lead and repair or excision of tricuspid valve).
 - Recurrent mycotic emboli.

Prosthetic valve endocarditis

Conventionally divided into early (<2 months post-operatively) and late (>2 months post-operatively).

Early prosthetic valve endocarditis

- Most commonly due to staphylococci, Gram-negative bacilli, diphtheroids, or fungi.
- Generally, infection has begun either perioperatively or in the immediate post-operative period.
- Often a highly destructive, fulminant infection, with valve dehiscence, abscess formation, and rapid haemodynamic deterioration.
- Discuss with surgeons early. They commonly require re-operation. Mortality is high (45–75%).

Late prosthetic valve endocarditis

- The pathogenesis is different. Abnormal flow around the prosthetic valve ring produces microthrombi and non-bacterial thrombotic vegetations (NBTVs), which may be infected during transient bacteraemia. The source is commonly dental or urological sepsis or indwelling venous lines.
- Common organisms are coagulase-negative staphylococci, *S. aureus*, *S. viridans*, or enterococci.
- Frequently needs surgical intervention, and this carries a high mortality, but less than for early PVE.
- It may be possible to sterilize infections on bioprostheses with IV antibiotics only. Surgery (🔪 Surgery for IE, pp. 114–15) may then be deferred.

Surgery for IE

Discuss early with the regional cardiothoracic centre—immediate intervention may be appropriate.

- Surgical intervention may be necessary either during active infection or later because of the degree of valve destruction. Optimal timing depends on a number of factors:
 - Haemodynamic tolerance of lesion.
 - Outcome of the infection.
 - Presence of complications.
- Choice of antimicrobial therapy should be modified, depending on microbiological results from intraoperative specimens. Samples should be sent for culture, staining, immunological testing, and PCR, depending on the suspected organism.
- Duration of antimicrobial treatment is dependent on the clinical picture:
 - Culture-negative operative specimens: 2–3 weeks for valve infection and 3–4 weeks for abscess.
 - Culture-positive operative specimens: 3–4 weeks for valve infection and 4–6 weeks for abscess.
- Timing is dictated by the clinical picture. Indications for urgent surgery are listed in Box 1.27. In patients with neurological injury, surgery should be delayed to avoid intracranial haemorrhage if cardiac function permits (embolic infarct: delay 10–14 days; haemorrhage: 21–28 days and when ruptured mycotic aneurysms have been repaired).
- Box 1.27 summarizes the absolute and relative indications for surgery.

Haemodynamic tolerance of lesion

- If the patient is haemodynamically stable, surgery may be delayed until after the antibiotic course is completed. Final management depends on the valve affected, the degree of destruction, and its effect on ventricular function. Severe AR and MR usually require surgery; tricuspid regurgitation, if well tolerated, is managed medically.
- Decompensation (severe CCF or low cardiac output syndrome with functional renal failure) may respond to surgery, but mortality is high.
- 'Metastable' patients who have been successfully treated after an episode of acute decompensation should be considered for early operation after 2–3 weeks of antibiotic therapy.

Outcome of infection

- Persistence or relapse of infection (clinical and laboratory indices), despite appropriate antibiotics at an adequate dose, may be due to either a resistant organism or an abscess (paravalvular, extracardiac). Consider valve replacement if no extracardiac focus is found.
- The organism may influence the decision—consider early surgery for fungal endocarditis or PVE with *Escherichia coli* or *S. aureus*.

Presence of complications

Urgent surgery indications comprise:

- High-degree AV block.
- Perforation of interventricular septum.
- Rupture of the sinus of Valsalva aneurysm into the RV.
- Intracardiac abscess.
- Recurrent septic emboli.
- PVE, especially associated with an unstable prosthesis.

Box 1.27 Indications for surgery in infective endocarditis

Absolute indications

- Moderate to severe heart failure secondary to valve regurgitation.
- Unstable prosthesis.
- Uncontrolled infection: persistent bacteraemia, ineffective antimicrobial therapy—IE secondary to fungi, *Brucella*, *Pseudomonas aeruginosa* (especially aortic and mitral valve).
- *S. aureus* prosthetic infection, with an intracardiac complication.

Relative indications

- Perivalvular extension of infection.
- Poor response to *S. aureus* native valve infection.
- Relapse after adequate treatment.
- Large (>10mm), hypermobile vegetations.
- Persistent unexplained fever in culture-negative endocarditis.
- Endocarditis secondary to antibiotic-resistant enterococci.

Endocarditis prophylaxis

NB This is one regimen (after Leport *et al.*).³ Refer to your local policy. See Boxes 1.28 and 1.29.

Box 1.21 shows cardiac conditions at risk of IE. High and moderate risk requires prophylaxis; 'low' risk does not.

The regimen may be modified, depending on the 'degree of risk' (both patient- and procedure-related), as shown in Table 1.10.

Box 1.28 Procedures that require antibiotic prophylaxis

- Dental:
 - All procedures.
- Upper respiratory tract:
 - Tonsillectomy, adenoidectomy.
- GI:
 - Oesophageal dilatation or laser therapy.
 - Oesophageal surgery.
 - Sclerosis of oesophageal varices.
 - Endoscopic retrograde cholangiopancreatography (ERCP).
 - Abdominal surgery.
 - Barium enema.
 - Sigmoidoscopy $\pm$ biopsy.
- Urological:
 - Instrumentation of ureter or kidney.
 - Biopsy or surgery of prostate or bladder.

Box 1.29 Procedures for which the risk of IE is controversial

- Upper respiratory tract:
 - Bronchoscopy.
 - ET intubation.
- GI:
 - Upper GI endoscopy $\pm$ biopsy.
- Genital:
 - Vaginal hysterectomy or delivery.

References

3. Leport C, Horstkotte D, Burckhardt D (1995). Antibiotic prophylaxis from an international group of experts towards a European consensus. Group of Experts of the International Society for Chemotherapy. *Eur Heart J* 16(Suppl B):126–31.

Table 1.10 Antibiotic prophylaxis

	1 hour before	6 hours after
Minimal regimen		
No penicillin allergy	Amoxicillin 3g PO	No 2nd dose
Allergy to penicillin	Clindamycin 300–600mg PO	No 2nd dose
Maximal regimen		
No penicillin allergy	Amoxicillin 2g IV + Gentamicin 1.5mg/kg IM/IV Vancomycin 1g IV over 1h	1–1.5g PO No 2nd dose 1g IV at 12h
Allergy to penicillin	+ Gentamicin 1.5mg/kg IM/IV	No 2nd dose
Flexible modifications, depending on ‘degree of risk’		
• Additional doses after procedure. • Additional aminoglycosides. • Parenteral administration.		

Acute aortic regurgitation

Presentation

- Sudden, severe AR presents as cardiogenic shock and acute pulmonary oedema.
- The haemodynamic changes are markedly different from those seen in chronic AR. The previous normal-sized LV results in a smaller effective forward flow and higher LVEDP for the same degree of AR.
- Patients are often extremely unwell, tachycardic, and peripherally shut down, and often have pulmonary oedema. Unlike chronic AR, pulse pressure may be near normal.
- If available, ask for a history of previous valvular heart disease, hypertension, features of Marfan's syndrome, and risk factors for IE (see Box 1.21).
- Physical signs of severe AR include a quiet aortic closure sound (S2), an ejection systolic murmur over the aortic valve (turbulent flow), a high-pitched and short early diastolic murmur (AR), and a quiet S1 (premature closure of the MV).
- Examine specifically for signs of an underlying cause (see Box 1.30).
- Where there is no obvious underlying cause (e.g. acute MI), assume IE until proven otherwise.

Diagnosis

Based on a combination of clinical features and TTE and/or TOE.

Management

Acute AR is a surgical emergency, and all other management measures are only aimed at stabilizing the patient until urgent aortic valve replacement (AVR) can take place. The patient's clinical condition will determine the urgency of surgery (and mortality). Liaise immediately with local cardiologists.

General measures

- Admit the patient to intensive care or medical HDU.
- Give O₂; begin treating any pulmonary oedema with diuretics.
- Monitor blood gases; mechanical ventilation may be necessary.
- Blood cultures × 3 are essential (➡ IE: investigations, p. 105).
- Serial ECG: watch for developing AV block or conduction defects.

Specific measures

- Every patient must be discussed with the regional cardiothoracic centre.
- In the context of good systemic BP, vasodilators, such as sodium nitroprusside or hydralazine, may temporarily improve forward flow and relieve pulmonary oedema.
- Inotropic support may be necessary if hypotensive. However, inotropes are best avoided, as any increase in systemic pressures may worsen AR.
- All patients with haemodynamic compromise should have immediate or urgent AVR.
- IE: indications for surgery are given in Box 1.27.
- IABP must be avoided, as it will worsen AR.

Box 1.30 Causes of acute AR

- IE.
- Ascending aortic dissection.
- Collagen vascular disorders (e.g. Marfan's syndrome).
- Connective tissue diseases (large- and medium-vessel arteritis).
- Trauma.
- Dehiscence of a prosthetic valve.

Acute mitral regurgitation

Presentation

- Patients most commonly present with acute breathlessness and severe pulmonary oedema. Symptoms may be less severe or spontaneously improve, as LA compliance increases. There may be a history of previous murmur, angina, or MI.
- The signs are different to those seen in chronic MR, because of the presence of a non-dilated and relatively non-compliant LA. Acute MR results in a large LA systolic pressure wave (v-wave), and hence pulmonary oedema.
- Patients may be acutely unwell, with tachycardia, hypotension, peripheral vasoconstriction, and pulmonary oedema and a pan-systolic murmur of MR.
- Later in the illness, probably because of sustained high LA and pulmonary venous pressures, right heart failure develops.
- Examine for signs of any underlying conditions (see Box 1.31).
- The important differential diagnosis is a VSD. TTE and Doppler studies can readily differentiate between the two conditions. Alternatively, if Echo is not available, PA catheterization in acute MR will exclude the presence of a left-to-right shunt and the PCWP trace will demonstrate a large v-wave.
- Where there is no obvious underlying cause (e.g. acute MI), assume the patient has IE until proven otherwise.

Diagnosis

Based on a combination of clinical features and Echo. TTE can readily diagnose and quantify MR. It also provides information on LV status (in particular, regional wall motion abnormalities which can give rise to MR). TOE can provide specific information about the aetiology of valve dysfunction, including papillary muscle rupture and MV leaflet (anterior and posterior) structural abnormalities. This information will be vital for a decision regarding definitive management.

General measures

- Admit the patient to intensive care or medical HDU.
- Give O₂; begin treating any pulmonary oedema with diuretics.
- Monitor blood gases; mechanical ventilation may be necessary.
- Blood cultures × 3 are essential (➡ IE: investigations, p. 105).
- If present, MI should be treated in the standard manner.

Specific measures

- Pulmonary oedema may be very resistant to treatment.
- In the presence of good BP, reduction in preload (GTN infusion) and afterload, especially with ACEIs, is important. Systemic vasodilators, such as hydralazine (12.5–100mg tds), can also be added in.
- An IABP will help decrease the LVEDP and also increase coronary blood flow.

- Patients may require inotropic support. There are multiple combinations, and the aetiology of MR, haemodynamic status, and local policy/expertise should dictate the choice of agent.
- CPAP and intubation and positive pressure ventilation are extremely useful and must be considered in all severe and/or resistant cases.
- Haemodynamic disturbance and severe pulmonary oedema in the context of acute MR is a surgical emergency.
- IE: indications for surgery are given under ➡ Surgery for IE, pp. 114–15.
- Post-infarct MR: management depends upon the patient's condition following resuscitation. Patients who are stabilized may have mitral valve replacement (MVR) deferred because of the risks of surgery in the post-infarct patient. Their preoperative management should consist of diuretics and vasodilators, including ACEIs if tolerated. Advise patients regarding endocarditis prophylaxis.

Box 1.31 Causes of acute MR

- IE.
- Papillary muscle dysfunction or rupture (see ➡ Acute mitral regurgitation post-MI, p. 36).
- Rupture of chordae tendinae (e.g. infection, myxomatous degeneration, SLE).
- Trauma (to leaflets, papillary muscle, or chordae).
- Prosthetic valve malfunction (e.g. secondary to infection).
- LA myxoma.
- Acute rheumatic fever.
- Collagen vascular disorders (e.g. Marfan's syndrome).
- Connective tissue diseases (large- and medium-vessel arteritis).

Deep vein thrombosis (DVT): assessment

Presentation

- Most commonly asymptomatic. Minor leg discomfort or isolated swelling (>65%) in the affected limb are the most common clinical features. Breathlessness or chest pain may be secondary to PE.
- Signs include erythema and swelling of the leg, dilated superficial veins, and calf discomfort on dorsiflexion of the foot (Homan's sign—this is nowadays rarely used, in view of the risk of dislodging and embolization of a clot). The thrombus may be palpable as a fibrous cord in the popliteal fossa. Confirm the presence of swelling (>2cm) by measuring the limb circumference 15cm above and 10cm below the tibial tuberosity.
- In all cases of leg swelling, abdominal and rectal (and pelvic in women) examination must be carried out to exclude an abdominal cause.

Risk factors for DVT

Procoagulant states

Congenital

- Factor V Leiden.
- Antithrombin III deficiency.
- Protein C deficiency.
- Protein S deficiency.

Acquired

- Malignant disease (~5%).
- Antiphospholipid syndrome.
- Myeloproliferative disorders.
- Oral contraceptive pill (especially with factor V Leiden mutation).
- Nephrotic syndrome (via renal AT III losses).
- Homocystinuria.
- Paroxysmal nocturnal haemoglobinuria.

Venous stasis

- Immobility (e.g. long journeys).
- Recent surgery.
- Pelvic mass.
- Pregnancy or recent childbirth.
- Severe obesity.

Miscellaneous

- Hyperviscosity syndromes (see ➡ Hyperviscosity syndrome, p. 654).
- Previous DVT or PE.
- Family history of DVT/PE.

Investigations

- Venous compression ultrasonography of leg veins is largely replacing venography as the initial investigation of choice. It is quick and non-invasive, with a sensitivity and specificity of >90%, and does not carry a risk of contrast allergy or phlebitis. It can simultaneously assess the extent of proximal progression of the thrombus, in particular extension into pelvic vessels.
- D-dimers have a high negative predictive value for DVT. A low clinical probability of DVT and a negative D-dimer might not require further investigation; however, chronic DVT might have normal D-dimer results. A positive D-dimer result should be followed by ultrasonography.

- Venography: use if results uncertain and clinical suspicion is high.
- Consider baseline investigations—FBC, U&Es, ECG, CXR, urinalysis, and pulse oximetry ($\pm$ ABG)—on all patients.
- If appropriate, look for an underlying cause.
 - Coagulation screen.
 - Procoagulant screen: refer to the local screening policy and get haematology advice (e.g. CRP, ESR, protein C and S, antithrombin III levels, factor V Leiden mutation, autoantibody screen, Igs and immunoelectrophoretic strip, anticardiolipin antibody, Ham's test, etc.).
 - Screen for malignancy: ultrasound (US) $\pm$ CT (abdomen and pelvis), CXR, LFTs, prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), CA-125, CA-19.9, β -human chorionic gonadotrophin (HCG), etc.

For the Wells rule to estimate the probability of DVT, see Table 1.11.

Table 1.11 Wells rule to estimate the probability of DVT*

Clinical feature	Score
Active cancer (including treatment up to 6 months previously)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremity	1
Recently bedridden for >3 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire limb swollen	1
Calf swelling by >3cm when compared with the asymptomatic leg	1
Pitting oedema (greater in the symptomatic leg)	1
Dilated collateral superficial veins (non-varicose)	1
Previously documented DVT	1
Alternative diagnosis as likely or more possible than that of DVT	-2
Clinical probability of DVT with score**	
Score >3	High
Score 1–2	Moderate
Score <1	Low

* Reprinted from *The Lancet*, 350, Wells PS, et al. 'Value of assessment of pretest probability of deep-vein thrombosis in clinical management', 1795–8, Copyright (1997), with permission from Elsevier.

** Source: data from Oudega R, et al. (2005). *Ann Intern Med* 143: 101.

DVT: management

- If there is a high clinical suspicion of DVT, start empiric anticoagulation with LMWH. (Stop this if subsequent investigations are negative.)
- Below-knee DVT: treat with compression stockings and SC prophylactic doses of LMWH until mobile, to deter proximal propagation of the thrombus.
- Above-knee DVT: thrombi within the thigh veins warrant full anticoagulation with LMWH/UFH and subsequently oral anticoagulant.
- See management algorithm in Fig. 1.10.

Anticoagulation

Heparin

- LMWHs have now superseded UFH for both DVT and PE.
- Treat with LMWH before starting oral anticoagulation.
- LMWH are administered primarily as a once-daily SC injection, and the dosage is determined by patient weight.

Warfarin

- Always start LMWH before starting warfarin and continue until the INR is within therapeutic range. Protein C (a vitamin K-dependent anticoagulant) has a shorter half-life than the other coagulation factors and levels fall sooner, resulting in a transient procoagulant tendency.
- Continue warfarin (INR 2–2.5) for 3 months (this varies, depending on the cause of DVT, from 6 weeks to life).
- If recurrent DVT, or patient is at high risk of recurrence, consider life-long anticoagulation.

Novel anticoagulants

Direct acting oral anticoagulants (dabigatran, apixaban, rivaroxaban and edoxaban) are licensed for treatment of DVT or PE and do not require routine testing.

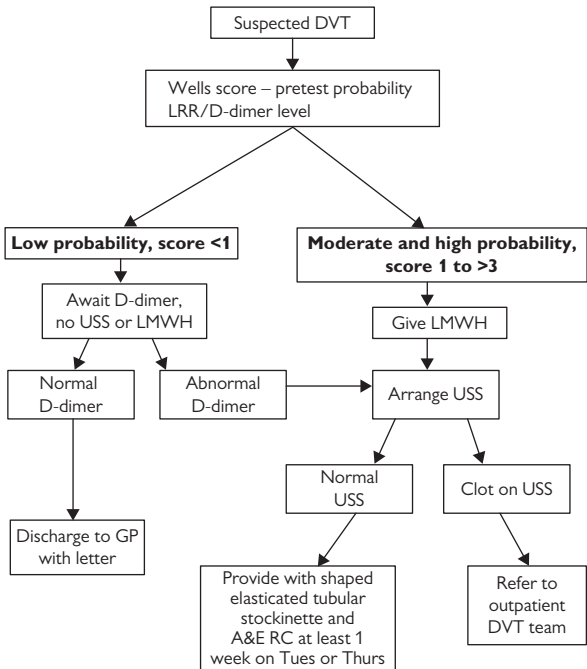
- Dabigatran and edoxaban should be started after 5 days of treatment with LMWH. The oral anticoagulant and LMWH should not be given together (see *BNF* for details).
- Apixaban and rivaroxaban do not require LMWH treatment before use, but require an initial period of treatment with a higher dose of the oral anticoagulant followed by a lower maintenance dose (see *BNF* for details).

Thrombolysis

- This should be considered for recurrent, extensive proximal venous thrombosis (e.g. femoral or iliac veins), as it is more effective than anticoagulation alone in promoting clot dissolution and produces a better clinical outcome. Given the lack of evidence base for this approach, an experienced clinician should be involved in this decision.
- Catheter-directed thrombolytic therapy (rtPA or SK) is superior to systemic thrombolysis.
- One approach is SK 250 000U over 30min, then 100 000U every hour for 24–72h (see data sheet). For contraindications to thrombolysis, see  STEMI: thrombolysis 2, pp. 24.

Further management

- Women taking the combined oral contraceptive pill (OCP) should be advised to stop this.
- If there are contraindications to anticoagulation, consider the insertion of a caval filter to prevent PE; however, such filters are best removed after 2 weeks to prevent long-term peripheral oedema from venous stasis.
- All patients should be treated with thigh-high compression stockings to try to reduce symptomatic venous distension when mobilizing.



Notes

1. Patients who are pregnant or who have previously had a DVT should be in the moderate to high group.
2. Patients who attend after hours should return to the CDU the following morning for a scan. Not all need LMWH.

Fig. 1.10 DVT management algorithm.

Pulmonary embolism (PE): assessment

Symptoms

- Classically presents with sudden-onset, pleuritic chest pain, associated with breathlessness and haemoptysis. Additional symptoms include postural dizziness or syncope.
- Massive PE may present as cardiac arrest [particularly with electromechanical dissociation (EMD)] or shock.
- Presentation may be atypical, i.e. unexplained breathlessness or unexplained hypotension or syncope only.
- PEs should be suspected in all breathless patients with risk factors for DVT or with clinically proven DVT (➡ DVT: management, pp. 124–5).
- Recurrent PEs may present with chronic pulmonary hypertension and progressive right heart failure.

Signs

- Examination may reveal tachycardia and tachypnoea only. Look for postural hypotension (in the presence of raised JVP).
- Look for signs of raised right heart pressures and cor pulmonale (raised JVP with prominent 'a' wave, tricuspid regurgitation, parasternal heave, RV S3, loud pulmonary closure sound with wide splitting of S2, pulmonary regurgitation).
- Cyanosis suggests a large PE.
- Examine for a pleural rub (may be transient) or effusion.
- Examine lower limbs for obvious thrombophlebitis.
- Mild fever ($>37.5^{\circ}\text{C}$) may be present. There may be signs of coexisting COPD.

Causes

- Frequently secondary to DVT (leg $>>$ arm; ➡ DVT: management, pp. 124–5).
- Other causes:
 - Rarely secondary to RV thrombus (post-MI).
 - Septic emboli (e.g. tricuspid endocarditis).
 - Fat embolism (post-fracture).
 - Air embolism (venous lines, diving).
 - Amniotic fluid.
 - Parasites.
 - Neoplastic cells.
 - Foreign materials (e.g. venous catheters).

Prognostic features

The prognosis in patients with PEs varies greatly, associated in part with any underlying condition. Generally worse prognosis is associated with larger PEs; poor prognostic indicators include:

- Hypotension.
- Hypoxia.
- ECG changes (other than non-specific T-wave changes).

Practice points

- A normal D-dimer excludes a PE with ~95% accuracy, but a positive D-dimer can be secondary to other disorders.

PE: investigations 1

General investigations

- **ABG:** a normal ABG does not exclude a PE. $\downarrow P_aO_2$ is invariable with larger PEs. Other changes include mild respiratory alkalosis and $\downarrow P_aCO_2$ (due to tachypnoea) and metabolic acidosis (secondary to shock).
- **ECG:** commonly shows sinus tachycardia and non-specific ST- and T-wave changes in the anterior chest leads. The classical changes of acute cor pulmonale, such as $S_1Q_3T_3$, right axis deviation, or RBBB, are only seen with massive PE. Less common findings include atrial flutter or AF.
- **CXR:** may be normal, and a near-normal chest film in the context of severe respiratory compromise is highly suggestive of a PE. Less commonly may show focal pulmonary oligemia (Westermark's sign), a raised hemidiaphragm, a small pleural effusion, wedge-shaped shadows based on the pleura, sub-segmental atelectasis, or dilated proximal PAs.
- **Blood tests:** there is no specific test. FBC may show neutrophil leucocytosis; mildly elevated CK, troponin, and bilirubin may be seen.
- **Echo/TOE:** insensitive for diagnosis but can exclude other causes of hypotension and raised right-sided pressures (e.g. tamponade, RV infarction; ➡ Right ventricular infarction, p. 28). In PE, it might show RV dilatation and global hypokinesia, with sparing of the apex (McConnell's sign), and PA dilatation. Doppler may show tricuspid/pulmonary regurgitation, allowing estimation of RV systolic pressure. Sometimes, in bigger PE, the thrombus in the PA may be visible.

For underlying causes, see Box 1.32.

Specific investigations

D-dimer

- A highly sensitive, but non-specific, test in acute PE.
- Useful in ruling out PE in patients with low or intermediate probability.
- Results can be affected by advancing age, pregnancy, trauma, surgery, malignancy, and inflammatory states.

Ventilation/perfusion lung scanning

A perfusion lung scan (with IV technetium-99-labelled albumin) should be performed in all suspected cases of PE. A ventilation scan (inhaled xenon-133) in conjunction increases the specificity by assessing whether the defects in the ventilation and perfusion scans 'match' or 'mismatch'. Pre-existing lung disease makes interpretation difficult.

- A normal perfusion scan rules out significant-sized PE and is reported as low probability for PE.
- Abnormal scans are reported as medium or high probability:
 - A high probability scan is strongly associated with PE, but there is a significant minority of false positives.
 - A low probability scan with low clinical suspicion of PE should prompt a search for another cause for the patient's symptoms.
 - If the clinical suspicion of PE is high and the scan is of low or medium probability, alternative investigations are required [usually computed tomography pulmonary angiogram (CTPA) or bilateral leg ultrasound scan (USS)].

Box 1.32 Investigations for an underlying cause for PEs

- USS deep veins of legs.
- USS abdomen and pelvis (? occult malignancy/pelvic mass).
- CT abdomen/pelvis.
- Screen for inherited procoagulant tendency (e.g. protein C, protein S, antithrombin III, factor V Leiden).
- Autoimmune screen [anticardiolipin antibody, anti-nuclear antibodies (ANA)].
- Biopsy of suspicious lymph nodes/masses.

PE: investigations 2

CTPA

- This is the recommended initial lung imaging modality in patients with non-massive PE.
- Allows direct visualization of emboli, as well as other potential parenchymal disease, which may provide an alternative explanation for symptoms.
- Sensitivity and specificity are high (>90%) for lobar PAs, but not so high for segmental and sub-segmental PAs.
- A patient with a positive CTPA does not require further investigation for PE.
- A patient with a negative CTPA in the context of a high/intermediate probability of a PE should undergo further investigation.

Evaluation of leg veins with USS

- Not very reliable. Almost half of patients with PE do not have evidence of a DVT and therefore, a negative result cannot rule out a PE.
- Useful second-line investigation as an adjunct to CTPA and V/Q scan.
- Outcome studies have demonstrated that it would be safe not to anticoagulate patients with a negative CTPA and lower limb USS who have an intermediate/low probability of a PE.

Pulmonary angiography

- Is the 'gold standard' investigation.
- It is indicated in patients in whom a diagnosis of embolism cannot be established by non-invasive means. Look for sharp cut-off of vessels or obvious filling defects.
- An invasive investigation, and can be associated with 0.5% mortality.
- If there is an obvious filling defect, the catheter, or a guidewire passed through the catheter, may be used to disobliterate the thrombus.
- After angiography, the catheter may be used to give thrombolysis directly into the affected PA (➔ PE: management 1, p. 132).
- The contrast can cause systemic vasodilatation and haemodynamic collapse in hypotensive patients.

Magnetic resonance pulmonary angiography

- Results are comparable to pulmonary angiography in preliminary studies.
- It can simultaneously assess ventricular function.

Fig. 1.11 summarizes one proposed pathway for investigation of potential PE patients.

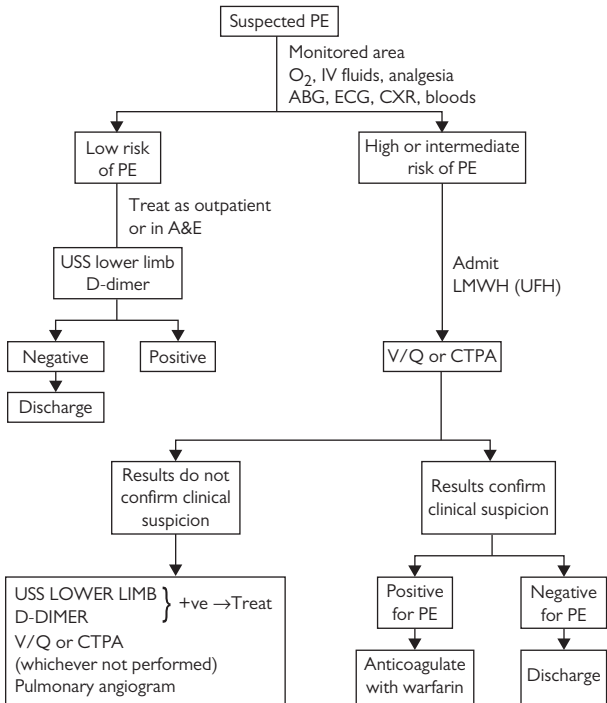


Fig. 1.11 Proposed pathway for investigation of patients with suspected PE.

PE: management 1

1. Stabilize the patient

- Unless an alternative diagnosis is made, the patient should be treated as for a PE until this can be excluded.
- Monitor cardiac rhythm, pulse, BP, and respiratory rate (RR) every 15min with continuous pulse oximetry and a cardiac monitor. Ensure full resuscitation facilities are available.
- Obtain venous access and start IV fluids (crystalloid or colloid).
- Give maximal inspired O₂ via face mask to correct hypoxia. Mechanical ventilation may be necessary if the patient is tiring (beware of cardiovascular collapse when sedation is given for ET intubation).
- Give LMWH or UFH to all patients with high or intermediate risk of PE until diagnosis is confirmed. A meta-analysis of multiple trials has shown LMWH to be superior to UFH, with a reduction in mortality and bleeding complications. For doses, consult the local formulary.
- If there is evidence of haemodynamic instability (systemic hypotension, features of right heart failure) or cardiac arrest, patients may benefit from thrombolysis with rtPA or SK—beware as doses used are different from treatment of STEMI (see Box 1.33).

2. Analgesia

- Patients may respond to oral NSAIDs (remember gastric protection, as these patients are also anticoagulated).
- Opiate analgesia to be used with caution. The vasodilatation caused by these drugs may precipitate or worsen hypotension. Give small doses (1–2mg diamorphine IV) slowly. Hypotension should respond to IV colloid.
- Avoid IM injections (anticoagulation and possible thrombolysis).

3. Investigations with a view to a definite diagnosis

See ➡ PE: investigations 1, p. 128 and ➡ PE: investigations 2, p. 130.

4. Anticoagulate

- Patients with a positive diagnosis must undergo anticoagulation with warfarin (or one of the newer licensed novel oral anticoagulants—this will depend on local protocols). There should be a period of overlap with LMWH/UFH until INR values are therapeutic. Target INR is 2–3 for most cases (see Box 1.34).
- Standard duration of anticoagulation is:
 - 4–6 weeks for temporary risk factor.
 - 3 months for first idiopathic cases.
 - At least 6 months for other cases.
- With recurrent events and underlying predisposition to thromboembolic events (e.g. antiphospholipid antibody syndrome), life-long anticoagulation may be needed (as well as higher target INR >3).

Box 1.33 Dosage of thrombolytic agents for PE

- Alteplase: 100mg over 2h or 0.6mg/kg over 15min (maximum of 50mg), followed by heparin.
- SK: 250 000U over 30min, followed by 100 000U/h infusion for 24h.

Box 1.34 Management key points: PE

- O₂.
- Start LMWH when PE is suspected.
- Start warfarin when PE is confirmed; continue LMWH until INR is therapeutic (2–3).
- Analgesia.
- IV fluids if hypotensive.
- If there is evidence of haemodynamic instability: consider thrombolysis.

PE: management 2

Cardiac arrest

(Also see ➡ Universal treatment algorithm, pp. 8–9.)

- Massive PE may present as cardiac arrest with EMD. Exclude the other causes of EMD (➡ Universal treatment algorithm, pp. 8–9).
- Chest compressions may help break up the thrombus and allow it to progress more distally, thereby restoring some cardiac output.
- If clinical suspicion of PE is high and there is no absolute contraindication to thrombolysis, give rtPA [similar in dose to STEMI, with a maximum of 50mg (see Box 1.33), followed by heparin].
- If cardiac output returns, consider pulmonary angiography or inserting a PA catheter to try to mechanically disrupt the embolus.

Hypotension

The acute increase in pulmonary vascular resistance (PVR) results in RV dilatation and pressure overload, which mechanically impairs LV filling and function. Patients require a higher than normal right-sided filling pressure but may be worsened by fluid overload.

- Insert an internal jugular sheath prior to anticoagulation. This can be used for access later, if necessary.
- If hypotensive, give colloid (e.g. 500mL of Haemaccel® stat).
- If hypotension persists, invasive monitoring and/or inotropic support is required. The JVP is a poor indicator of left-sided filling pressures in such cases. Adrenaline is the inotrope of choice.
- Femoro-femoral cardiopulmonary bypass or extracorporeal membrane oxygenation in a specialized centre may be used to support the circulation until thrombolysis or surgical embolectomy can be performed.
- Pulmonary angiography in a hypotensive patient is hazardous, as the contrast may cause systemic vasodilatation and cardiovascular collapse.

Pulmonary embolectomy

- In patients who have contraindications to thrombolysis and are in shock requiring inotropic support, there may be a role for embolectomy if appropriate skills are on site.
- This can be performed percutaneously in the catheterization laboratory using a number of devices or surgically on cardiopulmonary bypass.
- Percutaneous procedures may be combined with peripheral or central thrombolysis.
- Seek specialist advice early. Best results are obtained before onset of cardiogenic shock.
- Radiological confirmation of extent and site of embolism is preferable before thoracotomy.
- Mortality is ~25–30%.

Inferior vena cava filter

- Infrequently used, as little to suggest improved short- or long-term mortality.
- Filters are positioned percutaneously and, if possible, patients must remain anticoagulated to prevent further thrombus formation.
- Most are positioned infrarenally (bird's nest filter) but can also be suprarenal (Greenfield filter).
- Indications for inferior vena cava (IVC) filter use include:
 - Anticoagulation contraindicated, e.g. active bleeding, heparin-induced thrombocytopenia, planned intensive chemotherapy
 - Anticoagulation failure despite adequate therapy
 - Prophylaxis in high-risk patients, e.g. progressive venous thrombosis, severe pulmonary hypertension.

Fat embolism

Commonly seen in patients with major trauma. There is embolization of fat and microaggregates of platelets, RBCs, and fibrin in systemic and pulmonary circulation. Pulmonary damage may result directly from the emboli (infarction) or by chemical pneumonitis and ARDS (➡ Adult respiratory distress syndrome 1, p. 204).

Clinical features

- There may be a history of fractures, followed (24–48h later) by chest pain, breathlessness, cough, haemoptysis, confusion, and rash.
- Examination reveals fever (38–39°C), widespread petechial rash (25–50%), cyanosis, and tachypnoea. There may be scattered crepitations in the chest, although examination may be normal. Changes in mental state may be the first sign with confusion, drowsiness, seizures, and coma. Examine the eyes for conjunctival and retinal haemorrhages; occasionally, fat globules may be seen in the retinal vessels. Severe fat embolism may present as shock.

Investigations

- ABG: hypoxia and respiratory alkalosis (with low $P_a\text{CO}_2$), as for thromboembolic PE.
- FBC: thrombocytopenia, acute intravascular haemolysis.
- Coagulation: disseminated intravascular coagulation (DIC).
- U&Es and glucose: renal failure, hypoglycaemia.
- Ca^{2+} : may be low.
- Urine: microscopy for fat and dipstick for Hb.
- ECG: usually non-specific (sinus tachycardia; occasionally signs of right heart strain).
- CXR: usually lags behind the clinical course. There may be patchy bilateral air space opacification. Effusions are rare.
- CT head: consider if there is a possibility of head injury with expanding subdural or epidural bleed.

Differential diagnosis

Pulmonary thromboembolism, other causes of ARDS (➡ Adult respiratory distress syndrome 1, p. 204), septic shock, hypovolaemia, cardiac or pulmonary contusion, head injury, aspiration pneumonia, transfusion reaction.

Management

- Treat respiratory failure (➡ Respiratory failure: management, pp. 202–3). Give O_2 (maximal via face mask; CPAP and mechanical ventilation if necessary).
- Ensure adequate circulating volume and cardiac output. Central venous pressure (CVP) is not a good guide to left-sided filling pressures, and a PA catheter (Swan–Ganz) should be used to guide fluid replacement. Try to keep PCWP 12–15mmHg, and give diuretics if necessary. Use inotropes to support circulation, as required (➡ Adult respiratory distress syndrome 3, pp. 208–9).

- Aspirin, heparin, and dextran 40 (500mL over 4–6h) are of some benefit in the acute stages but may exacerbate bleeding from sites of trauma.
- High-dose steroids (methylprednisolone 30mg/kg q8h for three doses) have been shown to improve hypoxaemia,⁴ but steroids are probably most effective if given prophylactically.

References

4. Lindeque BG, Schoeman HS, Dommissie GF, Boeyens MC, Vlok AL (1987). Fat embolism syndrome and the fat embolism syndrome. A double-blind therapeutic study. *Bone Joint Surg Br* 69:128–31.

Hypertensive emergencies

Hypertensive crisis

Hypertensive crisis is defined as a severe elevation in BP [SBP >200mmHg, diastolic BP (DBP) >120mmHg]. Rate of change in BP is important. A rapid rise is poorly tolerated and leads to end-organ damage, whereas a gradual rise in a patient with existing poor BP control is tolerated better. Hypertensive crisis is classified as:

- *Hypertensive emergency* where a high BP is complicated by acute target organ dysfunction (see Box 1.35) and includes:
 - *Hypertensive emergency with retinopathy* where there is marked elevation in BP (classically DBP >140mmHg), with retinal haemorrhages and exudates (previously called accelerated hypertension), and
 - *Hypertensive emergency with papilloedema*, with a similarly high BP and papilloedema (previously called malignant hypertension).
- *Hypertensive urgency* where there is a similar rise in BP, but without target organ damage.

Conditions which may present with hypertensive emergency

- Essential hypertension.
- Renovascular hypertension: atheroma, fibromuscular dysplasia, acute renal occlusion.
- Renal parenchymal disease: acute glomerulonephritis, vasculitis, scleroderma.
- Endocrine disorders: pheochromocytoma, Cushing's syndrome, primary hyperaldosteronism, thyrotoxicosis, hyperparathyroidism, acromegaly, adrenal carcinoma.
- Eclampsia and pre-eclampsia.
- Vasculitis.
- Drugs: cocaine, amphetamines, monoamine oxidase inhibitor (MAOI) interactions, ciclosporin, β -blocker, and clonidine withdrawal.
- Autonomic hyperactivity in the presence of spinal cord injury.
- Coarctation of the aorta.

Presentation

- Occasionally, minimal non-specific symptoms such as mild headache and nosebleed.
- A small group of patients present with symptoms resulting from BP-induced microvascular damage:
 - Neurological symptoms: severe headache, nausea, vomiting, visual loss, focal neurological deficits, fits, confusion, intracerebral haemorrhage, coma.
 - Chest pain (hypertensive heart disease, MI, or aortic dissection) and CCF.
 - Symptoms of renal failure: renal impairment may be chronic (secondary to long-standing hypertension) or acute (from necrotizing vasculitis of malignant hypertension).

- Patients may present with hypertension as one manifestation of an underlying 'disease' (renovascular hypertension, CRF, CREST syndrome, pheochromocytoma, pregnancy).
- Examination should be directed at looking for evidence of end-organ damage, even if the patient is asymptomatic (heart failure, retinopathy, papilloedema, focal neurology).

Box 1.35 Examples of hypertensive emergencies

- Hypertensive emergency with retinopathy/papilloedema.
- Hypertensive encephalopathy.
- Hypertension-induced intracranial haemorrhage/stroke.
- Hypertension with cardiovascular complications.
- Aortic dissection (➡ Aortic dissection: assessment, p. 148–9).
- MI.
- Pulmonary oedema (➡ Pulmonary oedema: assessment, p. 92–3).
- Pheochromocytoma.
- Pregnancy-associated hypertensive complications.
- Eclampsia and pre-eclampsia.
- Acute renal insufficiency.
- Hypertensive emergency secondary to acute withdrawal syndromes (e.g. β -blockers, centrally acting antihypertensives).

Hypertensive emergencies: management

Priorities in management

- Confirm the diagnosis and assess the severity.
- Identify those patients needing specific emergency treatment.
- Plan long-term treatment.

Diagnosis and severity

- Ask about previous BP recordings, previous and current treatment, sympathomimetics, antidepressants, non-prescription drugs, and recreational drugs.
- Check the BP yourself, in both arms, after a period of rest and, if possible, on standing. Monitor the patient's BP regularly while they are in accident and emergency (A&E).
- Examine carefully for clinical evidence of cardiac enlargement or heart failure, peripheral pulses, renal masses, or focal neurological deficit. Always examine the fundi—dilate if necessary.

Investigations

All patients should have:

- FBC: MAHA with malignant hypertension.
- U&Es: renal impairment and/or $\downarrow K^+$ (diffuse intrarenal ischaemia and secondary hyperaldosteronism).
- Coagulation screen: DIC with malignant hypertension.
- CXR: cardiac enlargement:
 - Aortic contour (? dissection).
 - Pulmonary oedema.
- Urinalysis: protein and red cells $\pm$ casts.
- ECG: voltage criteria for LVH (see Box 1.36).

Other investigations, depending on the clinical picture and possible aetiology, include:

- 24-h urine collection:
 - Creatinine clearance.
 - Free catecholamines, metanephrines, or vanillyl mandelic acid (VMA).
- Echo: LVH, aortic dissection.
- Renal USS and Doppler: size of kidneys and renal artery stenosis.
- Magnetic resonance (MR) renal angiogram: renal artery stenosis.
- CT/MR brain: intracranial bleed.
- Drug screen: cocaine, amphetamine, others.

Box 1.36 Voltage criteria for LVH

- Tallest R (V4–V6) + deepest S (V1–V3) >40 mm.
- Tallest R (V4–V6) >27 mm.
- Deepest S (V1–V3) >30 mm.
- R in aVL >13 mm.
- R in aVF >20 mm.
- QRS complex >0.08 s (two small squares).
- Abnormal ST depression or T inversion in V4–V6.

Indications for admission

- DBP persistently ≥ 120 mmHg.
- Retinal haemorrhages, exudates, or papilloedema.
- Renal impairment.

Treatment principles

- Rapid reduction in BP must be avoided and can be very dangerous. This can result in cerebral and cardiac hypoperfusion (an abrupt change of $>25\%$ in BP will exceed cerebral BP autoregulation).
- Initial BP reduction of 25% to be achieved over 1–4h, with a less rapid reduction over 24h to a DBP of 100 mmHg.
- The only two situations where BP must be lowered rapidly are in the context of aortic dissection and MI.

Treatment

(Also see  Hypertensive emergencies: drug treatment, p. 142.)

- The majority of patients who are alert and otherwise well may be treated with oral therapy to lower BP gradually.
- For stable patients, first-line treatment should be with a low-dose calcium antagonist (e.g. amlodipine 5mg). Alternatively, a β -blocker, ACEI, or diuretic may be used.
- Urgent invasive monitoring (arterial line) prior to drug therapy is indicated for patients with:
 - Evidence of hypertensive encephalopathy.
 - Complications of hypertension (e.g. aortic dissection, acute pulmonary oedema, or renal failure).
 - Treatment of an underlying condition (e.g. glomerulonephritis, pheochromocytoma, CREST crisis).
 - Patients with persistent DBP ≥ 140 mmHg.
 - Eclampsia.
- Sublingual nifedipine must be avoided.

Conditions requiring specific treatment are listed in Box 1.37.

Long-term management

- Investigate, as appropriate, for an underlying cause.
- Select a treatment regimen that is tolerated and effective. Tell the patient why long-term therapy is important.
- Try to reduce all cardiovascular risk factors by advising the patient to stop smoking, giving appropriate dietary advice (cholesterol), and aiming for optimal diabetic control.
- Monitor long-term control and look for end-organ damage (regular fundoscopy, ECG, U&Es). Even poor control is better than no control.

Box 1.37 Conditions requiring specific treatment

- Accelerated and malignant hypertension ( Hypertensive emergency with retinopathy (accelerated and malignant hypertension), p. 144–5).
- Hypertensive encephalopathy ( Hypertensive encephalopathy, p. 146).
- Eclampsia.
- Pheochromocytoma.
- Hypertensive patients undergoing anaesthesia.

Hypertensive emergencies: drug treatment

(See Tables 1.12 and 1.13.)

Table 1.12 Drugs for the treatment of hypertensive emergencies: IV therapy

Drug	Dosage	Onset of action	Comments
Labetalol	20–80mg IV bolus q10min 20–200mg/min by IV infusion, increasing every 15min	2–5min	Drug of choice in suspected phaeochromocytoma (➡ Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, p. 654) or aortic dissection (➡ Aortic dissection: management 2, pp. 154–5). Avoid if there is LVF. May be continued PO (see below)
Nitroprusside	0.25–8 micrograms/kg/min IV infusion	Seconds	Drug of choice in LVF and/or encephalopathy
GTN	1–10mg/h IV infusion	2–5min	Mainly venodilatation. Useful in patients with LVF of angina
Hydralazine	5–10mg IV over 20min 50–300 micrograms/min IV infusion	10–15min	May provoke angina
Esmolol hydrochloride	500mg/kg/min IV loading dose 50–200 micrograms/kg/min IV infusion	Seconds	Short-acting β -blocker also used for SVTs
Phentolamine	2–5mg IV over 2–5min PRN	Seconds	Drug of choice in phaeochromocytoma (➡ Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, p. 654), followed by labetalol (PO) when BP controlled

NB It is dangerous to reduce the BP quickly. Aim to reduce the DBP to 100–110mmHg within 2–4h. Unless there are good reasons to commence IV therapy, always use oral medicines.

Table 1.13 Drugs for the treatment of hypertensive emergencies: oral therapy

Drug	Dosage	Comment
Amlodipine	5–10mg od	Minimal drug interactions
Atendol	50–100mg PO od	There are numerous alternative β -blockers—see <i>BNF</i>
Nifedipine	10–20mg PO q8h (q12h if slow release)	Avoid sublingual as the fall in BP is very rapid
Labetalol	100–400mg PO q12h	Use if phaeochromocytoma suspected. Safe in pregnancy
Hydralazine	25–50mg PO q8h	Safe in pregnancy
Minoxidil	5–10mg PO od	May cause marked salt and water retention. Combine with a loop diuretic (e.g. furosemide 40–240mg daily)
Clonidine	0.2mg PO, followed by 0.1mg hourly max. 0.8mg total for urgent therapy, or 0.05–0.1mg PO q8h, increasing every 2 days	Sedation common. Do not stop abruptly as there is a high incidence of rebound hypertensive crisis

NB Aim to reduce DBP to 100–110mmHg in 2–4h and normalize BP in 2–3 days.

Hypertensive emergency with retinopathy (accelerated and malignant hypertension)

This is part of a continuum of disorders characterized by hypertension (DBP often $>120\text{mmHg}$) and acute microvascular damage (seen best in the retina, but present in all organs). It may be difficult to decide whether the damage in some vascular beds is the cause or effect of hypertension. An example is in the context of acute glomerulonephritis.

- Accelerated hypertension (grade 3 retinopathy; see Box 1.38) may progress to malignant hypertension, with widespread necrotizing vasculitis of the arterioles (and papilloedema).
- Presentation is commonly with headache or visual loss and varying degrees of confusion. More severe cases present with renal failure, heart failure, microangiopathic haemolytic anaemia (MAHA), and DIC.

Management

- Transfer the patient to medical HDU/ITU.
- Insert an arterial line, and consider a central venous line if there is evidence of necrotizing vasculitis and DIC. Catheterize the bladder.
- Monitor the neurological state, ECG, and fluid balance.
- Aim to lower the DBP to 100mmHg or by $15\text{--}20\text{mmHg}$, whichever is higher, over the first 24h.
- Those with early features may be treated successfully with oral therapy (β -blockers, calcium channel blockers).
- Patients with late symptoms or who deteriorate should be given parenteral therapy, aiming for more rapid lowering of BP.
- If there is evidence of pulmonary oedema or encephalopathy, give furosemide $40\text{--}80\text{mg}$ IV.
- If there is no LVF, give a bolus of labetalol, followed by an infusion. For patients with LVF, nitroprusside or hydralazine is preferable.
- Consult the renal team for patients with ARF or evidence of acute glomerulonephritis ($>2+$ proteinuria, red cell casts). ARF is managed as described under  Acute kidney injury: management, pp. 298–9. Dopamine should be avoided, as it may worsen hypertension.
- Consider giving an ACEI. High circulating renin levels may not allow control of hypertension, which, in turn, causes progressive renal failure. ACEIs will block this vicious circle. There may be marked first-dose hypotension, so start cautiously.
- Haemolysis and DIC should recover with control of BP.

Hypertension in the context of acute stroke/ intracranial bleed

- Stroke/bleed may be the result of hypertension, or vice versa.
- In the acute setting, there is impaired autoregulation of cerebral blood flow and autonomic function. Small changes in systemic BP may result in catastrophic falls in cerebral blood flow.
- Systemic BP should not be treated, unless DBP >130mmHg and/or presence of severe cerebral oedema (with clinical manifestations).
- In most cases, BP tends to settle over 24–36h. If treatment is indicated, BP reduction principles, as listed earlier, must be adhered to and a combination of nitroprusside, labetalol, and calcium channel blockers can be used.
- Centrally acting agents must be avoided, as they cause sedation.
- In patients with subarachnoid haemorrhage (SAH), a cerebroselective calcium channel blocker, such as nimodipine, is used to decrease cerebral vasospasm.
- Systemic BP must also be treated if it qualifies with the principles listed earlier and/or if it remains elevated after 24h. There is no evidence that this reduces further events in the acute phase.

Box 1.38 Hypertensive retinopathy

- Grade 1: tortuous retinal arteries, silver wiring.
- Grade 2: AV nipping.
- Grade 3: flame-shaped haemorrhages and cottonwool spots.
- Grade 4: papilloedema.

Hypertensive encephalopathy

- Caused by cerebral oedema secondary to loss of cerebral autoregulatory function.
- Usually gradual onset and may occur in previously normotensive patients at BPs as low as 150/100mmHg. It is rare in patients with chronic hypertension and pressures are also much higher.

Symptoms

- Headache, nausea and vomiting, confusion, grade III and IV hypertensive retinopathy.
- Late features consist of focal neurological signs, fits, and coma.

Diagnosis

- A diagnosis of exclusion and other differential diagnoses must be ruled out (e.g. stroke, encephalitis, tumours, bleeding, vasculitis).
- History is helpful, particularly of previous seizures, SAH usually being sudden in onset, and strokes being associated with focal neurological deficit.
- Always exclude hypoglycaemia.
- Starting BP-lowering treatment for hypertension associated with a stroke can cause extension of the stroke.
- An urgent MRI or CT brain must be obtained to rule out some of the differential diagnoses.

Management

- The primary principle of BP control is to reduce DBP by 25% or reduce DBP to 100mmHg, whichever is higher, over a period of 1–2h.
- Transfer the patient to ITU for invasive monitoring (➡ Hypertensive emergency with retinopathy (accelerated and malignant hypertension), pp. 144–5).
- Monitor the neurological state, ECG, and fluid balance.
- Correct electrolyte abnormalities (K^+ , Mg^{2+} , Ca^{2+}).
- Give furosemide 40–80mg IV.
- Nitroprusside is the first-line agent, as it allows easy control of BP changes, despite its tendency to increase cerebral blood flow.
- Labetalol and calcium channel blockers are second-line agents and should be added in, if necessary.
- It is vital to avoid agents with potential sedative action such as β -blockers, clonidine, and methyldopa.
- In selected patients who are stable and present at the very early stages, oral therapy with a combination of β -blockers and calcium blockers may be sufficient.

Aortic dissection: assessment

Aortic dissection is a surgical/medical emergency and, untreated, has a 1-year mortality of >90%. Dissection begins with formation of a tear in the intima, and the force of the blood cleaves the media longitudinally to various lengths. Predisposing factors are summarized in Box 1.39.

Classification

There are three classifications, as illustrated in Fig. 1.12 (DeBakey, Stanford, and descriptive). Dissections involving the ascending and/or aortic arch are treated surgically, and those exclusive to the descending aorta are treated medically.

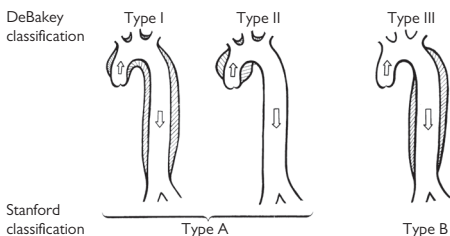


Fig. 1.12 Classification of aortic dissection.

Presentation

- **Chest pain:** classically abrupt onset of very severe, most commonly anterior, chest pain radiating to the interscapular region. Usually tearing in nature and, unlike the pain of MI, most severe at its onset. Pain felt maximally in the anterior chest is associated with ascending aortic dissection, whereas interscapular pain suggests dissection of the descending aorta. Patients often use adjectives such as 'tearing', 'ripping', 'sharp', and 'stabbing' to describe the pain.
- **Sudden death or shock:** usually due to aortic rupture or cardiac tamponade.
- **CCF:** due to acute aortic incompetence and/or MI from dissection extending into the coronary arteries (usually RCA).
- Patients may also present with symptoms and signs of occlusion of one of the branches of the aorta. Examples include:
 - Stroke or acute limb ischaemia: due to compression or dissection.
 - Paraplegia with deficits: spinal artery occlusion.
 - MI infarction: usually the RCA.
 - Renal failure and renovascular hypertension.
 - Abdominal pain: coeliac axis or mesenteric artery occlusion.
- Aortic dissection may be painless.
- Ask specifically about history of hypertension, previous heart murmurs or aortic valve disease, and previous CXRs that may be useful for comparison.

Examination

- This may be normal.
- Most patients are hypertensive on presentation. Hypotension is more common in dissections of the ascending aorta (20–25%) and

may be due to blood loss, acute aortic incompetence (which may be accompanied by heart failure), or tamponade (distended neck veins, tachycardia, pulsus paradoxus).

- Pseudohypotension may be seen if flow to either or both subclavian arteries is compromised. Look for unequal BP in the arms, and document the presence of peripheral pulses carefully. Absent or changing pulses suggest extension of the dissection.
- Auscultation may reveal aortic valve regurgitation and occasionally a pericardial friction rub. Descending aortic dissections may rupture or leak into the left pleural space, and the effusion results in dullness in the left base.
- Neurologic deficits may be due to carotid artery dissection or compression (hemiplegia) or spinal artery occlusion (paraplegia with sensory loss).

Differential diagnosis

- The chest pain may be mistaken for acute MI, and acute MI may complicate aortic dissection. Always look for other signs of dissection (see Box 1.37), as thrombolysis will be fatal.
- Severe chest pain and collapse may also be due to PE, spontaneous pneumothorax, acute pancreatitis, and penetrating duodenal ulcer.
- Pulse deficits without backache should suggest other diagnoses: atherosclerotic peripheral vascular disease, arterial embolism, Takayasu's arteritis, etc.
- Acute cardiac tamponade with chest pain is also seen in acute viral or idiopathic pericarditis and acute MI with external rupture.

Box 1.39 Conditions associated with aortic dissection

- Hypertension: smoking, dyslipidaemia, cocaine/crack.
- Connective tissue disorders:
 - Marfan's syndrome.*
 - Ehlers–Danlos syndrome.
- Hereditary vascular disorders: bicuspid aortic valve.
- Vascular inflammation:
 - Coarctation.
 - Giant cell arteritis.
 - Takayasu's arteritis.
 - Behçet's disease.
 - Syphilis.
- Deceleration trauma:
 - Car accident.
 - Falls.
- Chest trauma.
- Pregnancy.
- Iatrogenic.
 - Catheterization.
 - Cardiac surgery.

* Marfan's syndrome: arm span > height, pubis to sole > pubis to vertex, depressed sternum, scoliosis, high-arched palate, upward lens dislocation, thoracic aortic dilatation/aortic regurgitation, ↑ urinary hydroxyproline (some).

Practice points

Unilateral tongue weakness after a car crash with whiplash injury suggests carotid artery dissection.

Aortic dissection: investigations

General

- **ECG:** may be normal or non-specific (LVH, ST/T abnormalities). Look specifically for evidence of acute MI (inferior MI is seen if the dissection compromises the RCA ostium).
- **CXR:** may appear normal but, with hindsight, is almost always abnormal. Look for widened upper mediastinum, haziness or enlargement of the aortic knuckle, irregular aortic contour, separation ($>5\text{mm}$) of intimal calcium from outer aortic contour, displacement of trachea to the right, enlarged cardiac silhouette (pericardial effusion), and pleural effusion (usually on the left). Compare with previous films, if available.
- **Bloods:** baseline FBC, U&Es, cardiac enzymes, as well as cross-match. A novel monoclonal antibody assay to smooth muscle myosin heavy chains can accurately differentiate an acute dissection from an MI.

Diagnostic

- **Echocardiography:** TTE may be useful in diagnosing aortic root dilatation, AR, and pericardial effusion/tamponade. TOE is the investigation of choice, as it allows better evaluation of both the ascending aorta and descending aorta, may identify the origin of the intimal tear, allows evaluation of the origins of the coronary arteries in relation to the dissection flap, and provides information on aortic insufficiency. It is not good at imaging the distal ascending aorta and proximal arch.
- **MR angiography:** is the gold standard for diagnosing aortic dissection. It has all the positive features of TOE and, in particular, also provides accurate information on all segments of the ascending/arch/descending aorta, entry/exit sites, and branch vessels. Images can be displayed in multiple views, as well as reconstructed in three dimensions. However, there are a number of disadvantages, including: (1) availability of service out of hours and cost; (2) presence of metallic valves or pacemakers may preclude the patient from having an MRI; and (3) monitoring of unstable patients in the scanner can be difficult and unsafe.
- **Spiral (helical) CT with contrast:** allows three-dimensional display of all segments of the aorta and adjacent structures. True and false lumens are identified by differential contrast flow and enter and exit sites of the intimal flap, as well as pleural and pericardial fluids. However, it cannot demonstrate disruption of the aortic valve, which may be associated with ascending aortic dissection.
- **Angiography:** using the femoral or axillary approach, may demonstrate altered flow in the two lumens, aortic valve incompetence, involvement of the branches, and the site of the intimal tear. It is invasive and associated with a higher risk of complications in an already high-risk patient. It has largely been superseded by CT/MRI and TOE.

Selecting a diagnostic modality

(See Box 1.40.)

- Confirm or refute a diagnosis of dissection.
- Is the dissection confined to the descending aorta or does it involve the ascending aorta/aortic arch?
- Identify the extent, sites of enter and exit, and presence and absence of thrombus.
- To see whether there is AR, coronary involvement or pericardial effusions.

Box 1.40 Selecting a diagnostic modality

- Where available, TOE should be the first-line investigation. It is safe and can provide all the information necessary to take the patient to the operating theatre.
- If TOE is not available (or practical as the patient cannot cooperate) or if it fails to provide the necessary information, a spiral contrast CT should be performed.
- MRI should generally be reserved for follow-up images.
- Angiography is rarely used but is of value if other modalities have failed to provide a diagnosis and/or extensive information is needed on branch vessels.

Aortic dissection: management 1

Stabilize the patient

- If the diagnosis is suspected, transfer the patient to an area where full resuscitation facilities are readily available.
- Secure venous access with large-bore cannulae (e.g. green/grey Venflon®).
- Take blood for FBC, U&Es, and cross-match (10U).
- When the diagnosis is confirmed or in cases with cardiovascular complications, transfer to ITU; insert an arterial line (radial unless the subclavian artery is compromised when a femoral line is preferred), a central venous line, and a urinary catheter.
- Immediate measures should be taken to correct BP (➡ Aortic dissection: management 2, pp. 154–5).
- Adequate analgesia (diamorphine 2.5–10mg IV and metoclopramide 10mg IV).

Plan the definitive treatment

(See Box 1.41.)

This depends on the type of dissection (see Fig. 1.13) and its effects on the patient. General principles are:

- Patients with involvement of the ascending aorta should have emergency surgical repair and BP control.
- Patients with dissection limited to the descending aorta are managed initially medically with aggressive BP control.

However, this may change in the near future with emerging encouraging data from deployment of endovascular stent grafts.

Indications and principles for surgery

- Involvement of the ascending aorta.
- External rupture (haemopericardium, haemothorax, effusions).
- Arterial compromise (limb ischaemia, renal failure, stroke).
- Contraindications to medical therapy (AR, LVF).
- Progression (continued pain, expansion of haematoma on further imaging, loss of pulses, pericardial rub, or aortic insufficiency).

The aim of surgical therapy is to replace the ascending aorta, thereby preventing retrograde dissection and cardiac tamponade (main cause of death). The aortic valve may need reconstruction and resuspension, unless it is structurally abnormal (bicuspid or Marfan's) where it is replaced.

Indications and principles for medical management

Medical therapy is the treatment of choice for:

- Uncomplicated type B dissection.
- Stable isolated arch dissection.
- Chronic (>2 weeks' duration) stable type B dissection.

In all but those patients who are hypotensive, initial management is aimed at reducing systemic BP and myocardial contractility. The goal is to stop the spread of the intramural haematoma and to prevent rupture. The best guide is control of pain. Strict bed rest in a quiet room is essential.

Box 1.41 Management key points: aortic dissection

- Monitor haemodynamically in ITU.
- Adequate analgesia: diamorphine (+ metoclopramide).
- Type A (involving the ascending aorta): emergency surgical repair and BP control.
- Type B (involving the descending aorta): manage medically with BP control.
- Reduce BP (aim for systolic: 100–120mmHg): start on IV β -blocker (e.g. labetalol) if no contraindications.
- Resuscitate hypotensive patients with IV fluids.

Aortic dissection: management 2

Control blood pressure

Reduce SBP to 100–120mmHg.

- Start on IV β -blocker (if no contraindications), aiming to reduce the HR to 60–70bpm (see Table 1.14).
- Once this is achieved, if BP remains high, add a vasodilator such as sodium nitroprusside (see Table 1.14). Vasodilators in the absence of β -blockade may increase myocardial contractility and the rate of rise in pressure (dP/dt). Theoretically, this may promote extension of the dissection.
- Further antihypertensive therapy may be necessary, and other conventional agents such as calcium channel blockers, β -blockers, and ACEIs can be used.
- In patients with AR and CCF, myocardial depressants should not be given. Aim to control BP with vasodilators only.

Hypotension

May be due to haemorrhage or cardiac tamponade.

- Resuscitate with rapid IV volume (ideally colloid or blood, but crystalloid may be used also). A PA wedge catheter (Swan–Ganz) should be used to monitor the wedge pressure and guide fluid replacement.
- If there are signs of AR or tamponade, arrange for an urgent Echo and discuss with the surgeons.

Emerging indications and principles for interventional therapy

There are increasing reports and short case series demonstrating favourable outcome (prognostic as well as symptomatic) data on using endovascular stent grafts in the management of primarily type B and also, to a lesser extent, type A aortic dissections.

On the basis of current evidence, endovascular stent grafts should be considered to seal the entry to the false lumen and to enlarge the compressed true lumen in the following situations:

- Unstable type B dissection.
- Malperfusion syndrome (proximal aortic stent graft and/or distal fenestration/stenting of branch arteries).
- Routine management of type B dissection (under evaluation).

Cardiac tamponade

If the patient is relatively stable, pericardiocentesis may precipitate haemodynamic collapse and should be avoided. The patient should be transferred to the operating theatre for direct repair as urgently as possible. In the context of tamponade and EMD or marked hypotension, pericardiocentesis is warranted.

Long-term treatment

Must involve strict BP control.

Prognosis

- Mortality for untreated aortic dissection is roughly 20–30% at 24h and 65–75% at 2 weeks.
- For dissections confined to the descending aorta, short-term survival is better (up to 80%), but ~30–50% will have progression of dissection, despite aggressive medical therapy, and will require surgery.
- Operative mortality is in the order of 10–25% and depends on the condition of the patient preoperatively. Post-operative 5-year actuarial survival of up to 75% may be expected.

Table 1.14 Medical therapy of aortic dissection

β -blockade (aim for HR 60–70bpm)

Labetalol	20–80mg slow IV injection over 10min, then 20–200mg/h IV, increasing every 15min, 100–400mg PO q12h
Atenolol	5–10mg slow IV injection, then 50mg PO after 15min and at 12h, then 100mg PO daily
Propranolol	0.5mg IV (test dose), then 1mg every 2–5min up to max. 10mg; repeat every 2–3h 10–40mg PO 3–4 times daily

When HR 60–70bpm (or if β -blocker contraindicated), add:

Nitroprusside	0.25–8 micrograms/kg/min IV infusion
Hydralazine	5–10mg IV over 20min 50–300 micrograms/min IV infusion 25–50mg PO q8h
GTN	1–10mg/h IV infusion
Amlodipine	5–10mg PO od

Acute pericarditis: assessment

Presentation

- Typically presents as central chest pain, often pleuritic, relieved by sitting forward and can be associated with breathlessness.
- Other symptoms (e.g. fever, cough, arthralgia, rash, faintness/dizziness secondary to pain/ $\uparrow$ HR) may reflect the underlying disease (see Box 1.42).
- A pericardial friction rub is pathognomonic. This may be positional and transient and may be confused with the murmur of tricuspid regurgitation or MR.
- Venous pressure rises if an effusion develops. Look for signs of cardiac tamponade (➡ Cardiac tamponade: presentation, pp. 162–3).

Investigations

ECG

- May be normal in up to 10%.
- ‘Saddle-shaped’ ST-segment elevation (concave upwards), with variable T inversion (usually late stages) and PR-segment depression (opposite to P-wave polarity). Minimal lead involvement to be considered, typically including I, II, aVL, aVF, and V3–V6.
- ST segment is always depressed in aVR, frequently depressed or isoelectric in V1, and sometimes in depressed in V2.
- May be difficult to distinguish from acute MI. Features suggesting pericarditis are:
 - Concave ST elevation (versus convex).
 - All leads involved (versus a territory, e.g. inferior).
 - Failure of usual ST evolution and no Q waves.
 - No AV block, bundle branch block, or QT prolongation.
- Early repolarization (a normal variant) may be mistaken for pericarditis. In the former, ST elevation occurs in precordial and rarely in V6 or limb leads and is unlikely to show ST depression in V1 or PR-segment depression.
- Usually not helpful in diagnosing pericarditis post-MI.
- The voltage drops as an effusion develops, and in tamponade, there is electrical alternans, best seen in QRS complexes.

Echo

- May demonstrate a pericardial collection.
- Useful to monitor LV function in case of deterioration due to associated myopericarditis.
- We recommend every patient has an Echo prior to discharge to assess LV function.

Other investigations depend on the suspected aetiology

All patients should have:

- FBC and biochemical profile.
- ESR and CRP (levels rise proportionate to intensity of disease).
- Serial cardiac enzymes (CK, CK-MB, troponin). Elevations indicate sub-pericardial myocarditis.
- CXR (heart size, pulmonary oedema, infection).

Where appropriate

- Viral titres (acute + 2 weeks later) and obtain virology opinion.
- Blood cultures.
- Autoantibody screen (rheumatoid factor, ANA, anti-DNA, complement levels).
- TFTs.
- Fungal precipitins (if immunosuppressed), Mantoux test.
- Sputum culture and cytology.
- Diagnostic pericardial tap (culture, cytology).

Box 1.42 Causes of acute pericarditis

- Idiopathic.
- Infection [viral, bacterial, tuberculosis (TB), and fungal].
- Acute MI.
- Dressler's syndrome, post-cardiotomy syndrome.
- Malignancy (e.g. breast, bronchus, lymphoma).
- Uraemia.
- Autoimmune disease [e.g. SLE, RA, Wegener's, scleroderma, polyarteritis nodosa (PAN)].
- Granulomatous diseases (e.g. sarcoid).
- Hypothyroidism.
- Drugs (hydralazine, procainamide, isoniazid).
- Trauma (chest trauma, iatrogenic).
- Radiotherapy.

Acute pericarditis: management

General measures

- *Admit?* Depends on clinical picture. We recommend admission of most patients for observation for complications, especially effusions, tamponade, and myocarditis. Patients should be discharged when pain-free.
- *Bed rest.*
- *Analgesia:* NSAIDs are the mainstay. Ibuprofen is well tolerated and increases coronary flow (200–800mg qds). Aspirin is an alternative (600mg qds PO). Indometacin should be avoided in adults, as it reduces coronary flow and has marked side effects. Use PPI (lansoprazole 30mg od) to minimize GI side effects. Opioid analgesia may be required. Colchicine used as monotherapy or in addition to NSAIDs may help settle pain acutely and prevent recurrence.
- *Steroids:* these may be used if the pain does not settle within 48h [e.g. prednisolone enteric-coated (EC) 40–60mg PO od for up to 2 weeks, tapering down when pain settles]. Use in conjunction with NSAID, and taper steroids first before stopping NSAID. It is also of value if pericarditis secondary to autoimmune disorders.
- *Colchicine:* evidence suggests that, either used as monotherapy or in conjunction with NSAIDs, it may help to settle pain acutely and prevent relapses (1mg/day in divided doses). Stop if the patient develops diarrhoea and nausea (1mg stat, 500 micrograms q6h for 48h).
- *Pericardiocentesis:* this should be considered for significant effusion or if there are signs of tamponade (➔ Cardiac tamponade: presentation, pp. 162–3).
- *Antibiotics:* these should be given only if bacterial infection is suspected.
- *Oral anticoagulants:* should be discontinued (risk of haemopericardium). Patient should be given IV UFH, which is easier to reverse (IV protamine) if complications arise.

Bacterial pericarditis

- The most common pathogens are *Pneumococcus*, staphylococci, streptococci, Gram-negative rods, and *Neisseria* spp.
- Risk factors include pre-existing pericardial effusion (e.g. uraemic pericarditis) and immunosuppression [iatrogenic, lymphoma, leukaemia, human immunodeficiency virus (HIV)].
- The infection may have spread from mediastinitis, IE, pneumonia, or a sub-diaphragmatic abscess.
- Suspect in patients with high fever, night sweats, dyspnoea, and raised JVP (chest pain may be mild or absent); there may be other intrathoracic infection (e.g. pneumonia).
- If suspected, take blood cultures and start IV flucloxacillin (2g qds) and IV gentamicin or IV cefotaxime (2g tds). Adjust treatment when sensitivities known.
- Significant-sized pericardial collections should be drained to dryness, if possible. Send fluid for Gram and Ziehl–Neelsen (ZN) stain, fungal smear, and culture. Surgical drainage may be required for recurrent effusions.
- Patients with TB pericarditis are very prone to developing cardiac constriction. Steroids have not been shown to prevent this, but they do prevent progression once constrictive symptoms develop. Surgical pericardectomy may be required. Take advice from cardiologists and ID team.

Viral pericarditis

- Pathogens include Coxsackie A + B, echovirus, adenovirus, mumps, Epstein–Barr virus (EBV), varicella-zoster virus (VZV), cytomegalovirus (CMV), hepatitis B, and HIV.
- Usually a self-limiting illness (1–3 weeks) and can be seasonal. Common in young individuals with no associated cardiac history.
- Twenty to 30% develop recurrent pericarditis.
- Complications include recurrent pericarditis (20–30%), myocarditis, dilated cardiomyopathy, pericardial effusion and tamponade, and late pericardial constriction.
- Treatment is supportive (➡ Acute pericarditis: management, p. 158).

Uraemic pericarditis

This is an indication for urgent dialysis (see Box 4.3).

Dressler's syndrome, post-cardiotomy syndrome

- Complicates ~1% of acute MI and 10–15% of patients following cardiac surgery presenting 2–4 weeks later (up to 3 months later).
- Consists of recurrent pericarditis, fever, anaemia, high ESR, neutrophil leucocytosis, pleural effusions, and transient pulmonary infiltrates on CXR.
- Treat with bed rest, and NSAIDs (aspirin 600mg PO qds) and steroids for persisting symptoms (➡ Acute pericarditis: management, p. 158).
- Pericarditis following acute MI (➡ STEMI: complications, pp. 32–3).

Neoplastic pericarditis

- The 1-year survival of patients with malignant effusive pericarditis is $\leq 25\%$. Approach to treatment depends on the underlying malignancy and symptoms.
- Asymptomatic pericardial effusions do not require drainage. Treat the underlying malignancy ($\pm$ mediastinal radiotherapy). Recurrent effusions may need formation of a surgical pericardial window.
- Drainage is indicated for cardiac tamponade.

Myopericarditis

- Although it can occur with all cases of pericarditis, it is more common in the context of acquired immune deficiency syndrome (AIDS), vasculitis/connective tissue disorders, rheumatic fever, and TB infection.
- Clinical suspicion should be higher in the context of pericarditis accompanied by significant arrhythmia (especially ventricular) and features of LV dysfunction and sinus tachycardia out of proportion to the clinical picture (fever, pain, persistence over $>5-6$ days).
- Biochemical markers of myocardial injury are often positive (especially TnT or TnI).
- In the absence of heart failure, treatment is as for uncomplicated pericarditis. Steroids should be avoided, unless indicated as part of treatment for the underlying cause. Heart failure should be treated conventionally. Interferon can be used to treat enteroviral infections, and globulins for CMV.
- Pericardial effusions must be drained with care, as the effusion may be 'splinting' a dilated/myocarditic heart. Drainage can lead to rapid dilatation and cardiovascular collapse.
- Prognosis is generally good and most recover, unless there is severe LV impairment.

Cardiac tamponade: presentation

Cardiac tamponade occurs when a pericardial effusion causes haemodynamically significant cardiac compression. The presentation depends on the speed with which fluid accumulates within the pericardium. Acute tamponade may occur with 100–200mL in a relatively restricted pericardial sac. Chronic pericardial collections may contain up to 1000mL of fluid without clinical tamponade.

Causes

Acute tamponade

- Cardiac trauma.
- Iatrogenic:
 - Post-cardiac surgery.
 - Post-cardiac catheterization.
 - Post-pacing/EPS.
- Aortic dissection.
- Spontaneous bleed:
 - Anticoagulation.
 - Uraemia.
 - Thrombocytopenia.
- Cardiac rupture post-MI.

'Subacute' tamponade

- Malignant disease.
- Idiopathic pericarditis:
 - Uraemia.
- Infections:
 - Bacterial.
 - TB.
- Radiation.
- Hypothyroidism.
- Post-pericardotomy.
- SLE.

Presentation

- Patients commonly present either with cardiac arrest (commonly EMD) or with hypotension, confusion, stupor, and shock.
- Patients who develop cardiac tamponade slowly are usually acutely unwell, but not *in extremis*. Their main symptoms include:
 - Breathlessness, leading to air hunger at rest.
 - There may be a preceding history of chest discomfort.
 - Symptoms resulting from compression of adjacent structures by a large effusion (i.e. dysphagia, cough, hoarseness, or hiccough).
 - There may be symptoms due to the underlying cause (see Box 1.43).
 - Insidious development may present with complications of tamponade, including renal failure, liver and/or mesenteric ischaemia, and abdominal plethora.

Important physical signs

Most physical findings are non-specific. They include:

- Tachycardia (except in hypothyroidism and uraemia).
- Hypotension ($\pm$ shock) with postural hypotension.
- Raised JVP (often >10cm) with a prominent systolic x descent and an absent diastolic y descent (see Fig. 1.13). If the JVP is visible and either remains static or rises with inspiration, it indicates concomitant pericardial constriction (Kussmaul's sign).
- Auscultation may reveal diminished heart sounds. Pericardial rub may be present and suggests a small pericardial collection.
- Look for pulsus paradoxus (a decrease in the palpable pulse and SBP of >10mmHg on inspiration). This may be so marked that the pulse and Korotkoff sounds may be completely lost during inspiration. This can be

measured using a BP cuff (see Box 1.44) or an arterial catheter if *in situ* already. Other conditions that can cause pulsus paradoxus include acute hypotension, obstructive airways disease, and PE.

- Other physical signs include cool extremities (ears, nose), tachypnoea, hepatomegaly, and signs of the underlying cause for the pericardial effusion.

Box 1.43 Causes of hypotension with a raised JVP

- Cardiac tamponade.
- Constrictive pericarditis.
- Restrictive pericarditis.
- Severe biventricular failure.
- RV infarction.
- PE.
- Tension pneumothorax.
- Acute severe asthma.
- Malignant superior vena cava (SVC) obstruction and sepsis (e.g. lymphoma).

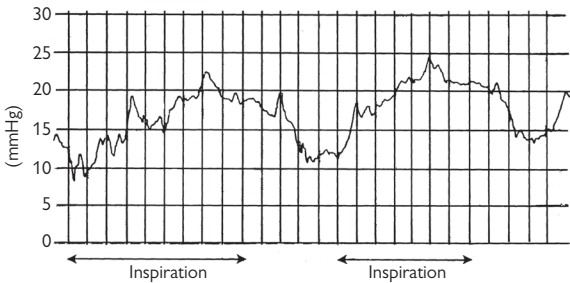


Fig. 1.13 Right atrial pressure (RAP) tracing in tamponade. There is a paradoxical rise in RAP during inspiration.

Box 1.44 Key point

To establish the presence of pulsus paradoxus non-invasively, inflate the BP cuff to 15mmHg above the highest systolic pressure. Deflate the cuff gradually until the first beats are heard and hold the pressure at that level, concentrating on the disappearance and reappearance of sounds with respiration (bump–bump, silence–silence, bump–bump, where noise reflects expiration). Continue to deflate slowly, paying attention to the same pattern until all beats are audible. The difference between the initial and final pressure should be >10mmHg.

Cardiac tamponade: management

Tamponade should be suspected in patients with hypotension, elevated venous pressure, falling BP, ↑HR and ↑RR (with clear chest), and pulsus paradoxus, especially if predisposing factors are present.

Investigations

- **CXR:** the heart size may be normal (e.g. in acute haemopericardium following cardiac trauma). With slower accumulation of pericardial fluid (>250mL), the cardiac silhouette will enlarge with a globular appearance. The size of the effusion is unrelated to its haemodynamic significance. Look for signs of pulmonary oedema.
- **ECG:** usually shows sinus tachycardia, with low-voltage complexes and variable ST-segment changes. With large effusions, 'electrical alternans' may be present with beat-to-beat variation in the QRS morphology resulting from movement of the heart within the pericardial effusion.
- **Echocardiography:** confirms the presence of a pericardial effusion. The diagnosis of tamponade is a clinical one. Echo signs highly suggestive of tamponade include:
 - Chamber collapse during diastole (RA, RV, RVOT).
 - Marked variation in transvalvular flow.
 - Dilated IVC, with little or no diameter change on respiration.
- If available, examine the CVP trace for the characteristic exaggerated x descent and absent y descent.

Management

Following confirmation of the diagnosis:

- While preparing for drainage of the pericardial fluid, the patient's circulation may temporarily be supported by loading with IV colloid (500–1000mL stat) and starting inotropes (i.e. adrenaline).
- In patients with an adequate BP, cautious systemic vasodilatation with hydralazine or nitroprusside, in conjunction with volume loading, may increase forward cardiac output. This is not to be recommended routinely, as it may cause acute deterioration.
- The effusion should be urgently drained (➡ Pericardial aspiration 1, pp. 814–15 for pericardiocentesis), guided by Echo or fluoroscopy. *In the event of circulatory collapse, drainage must happen immediately without imaging.*
- Surgical drainage is indicated if the effusion is secondary to trauma.
- Avoid intubation and positive pressure ventilation, as this reduces cardiac output.
- In patients with cardiac arrest, chest compression has little or no value, as there is no room for additional filling.
- Uraemic patients will also need dialysis.
- The cause of the effusion should be established (see Box 1.43). Pericardial fluid should be sent for cytology, microbiology (including TB), and, if appropriate, Hb, glucose, and amylase.

Further management is of the underlying cause.

Special cases

Recurrent pericardial effusion

In some cases, pericardial effusion recurs. This requires either a change in treatment of the underlying cause or a formal surgical drainage procedure such as a surgical pericardial window or pericardiectomy.

Low-pressure tamponade

Seen in the setting of dehydration. The JVP is not raised, RA pressure is normal, and tamponade occurs even with small volumes of pericardial fluid.

- The patient may respond well to IV fluids.
- If there is a significant pericardial collection, this should be drained.

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Extracardiac complications

- Polycythaemia:** chronic hypoxia stimulates erythropoietin production and erythrocytosis. The 'ideal' Hb level is ~17–18g/dL; some centres used to advocate regular venesection to control the haematocrit and prevent hyperviscosity syndrome (➡ Hyperviscosity syndrome, p. 654), although of late, in most centres, this is limited only to patients who have experienced a side effect relating to hyperviscosity (e.g. stroke). However, follow local guidelines and liaise with the local congenital heart disease cardiologist. Generally, consider phlebotomy only if moderate or severe symptoms of hyperviscosity are present and haematocrit is >65%. Remove 500mL of blood over 30–45min, and replace the volume simultaneously with 500–1000mL of saline, or salt-free dextran (if heart failure). Avoid abrupt changes in circulating volume. If hyperviscosity symptoms are the result of acute dehydration or iron deficiency, venesection is not required and the patient must be rehydrated and/or treated with iron.
- Renal disease and gout:** hypoxia affects glomerular and tubular function, resulting in proteinuria, reduced urate excretion, ↑urate reabsorption, and reduced creatinine clearance. Overt renal failure is uncommon. Try to avoid dehydration, diuretics, and radiographic contrast. Asymptomatic hyperuricaemia does not need treatment. Colchicine and steroids are first-line agents for treatment of acute gout. NSAIDs should be avoided.
- Sepsis:** patients are more prone to infection. Skin acne is common, with poor healing of scars. Skin stitches for operative procedures should be left in for 7–10 days longer than normal. Dental hygiene is very important due to the risk of endocarditis. Any site of sepsis may result in cerebral abscesses from metastatic infection or septic emboli.
- Thrombosis and bleeding:** multifactorial and caused by a combination of abnormal platelet function, coagulation abnormalities, and polycythaemia. Prothrombin time (PT) and aPTT values may be elevated and secondary to a fall in factors V, VII, VIII, and X. Both arterial and venous thromboses and haemorrhagic complications (e.g. petechiae, epistaxes, haemoptyses) can occur. Dehydration or oral contraceptives are risk factors for thrombotic events. Spontaneous bleeding is generally self-limiting. In the context of severe bleeding, general measures are effective, including platelet transfusion, FFP, cryoprecipitate, and vitamin K. Aspirin and other NSAIDs should generally be avoided to decrease chances of spontaneous bruising/bleeding.
- Primary pulmonary problems:** include infection, infarction, and haemorrhage from ruptured arterioles or capillaries.
- Stroke:** can be both thrombotic as well as haemorrhagic. Arterial thrombosis, embolic events (paradoxical emboli in right-to-left shunt), and injudicious phlebotomy lead to spontaneous thrombosis. Haemostasis problems (as indicated earlier), especially when combined with NSAIDs or formal anticoagulation, can lead to haemorrhagic stroke. Any injured brain tissue is also a nidus for intracranial infection/abscess formation.

- *Complications secondary to drugs, investigations, and surgery:* avoid abrupt changes in BP or systemic resistance. Contrast agents may provoke systemic vasodilatation and cause acute decompensation. They may also precipitate renal failure. Before non-cardiac surgery, try to optimize the haematocrit and haemostasis by controlled phlebotomy and replacement with dextran. High-flow O_2 is important before and after surgery. Extreme precaution with IV lines.
- *Arthralgia:* mainly due to hypertrophic osteoarthropathy. In patients with right-to-left shunt, megakaryocytes bypass the pulmonary circulation and become trapped in systemic vascular beds, promoting new bone formation.

Cardiac complications

- *CCF:* the aetiology can be complex and is often directly dependent on the underlying abnormality. Possibilities include valve dysfunction (calcification of an abnormal valve or secondary to supra- or subvalvular fibrosis and stenosis), ventricular dysfunction (hypertrophy, fibrosis, and failure), dysfunctioning surgical shunt, or pulmonary arteriolar disease and shunt reversal. Treat as usual, taking special care not to dehydrate the patient or precipitate acute changes in BP (➡ Congenital heart disease in adults 2, pp. 168–9).
- *Endocarditis:* the risk depends on the cardiac lesion and the pathogen (see Box 1.21). The recommended antibiotic prophylaxis regimen is given under ➡ Endocarditis prophylaxis, p. 116. Although the National Institute for Health and Care Excellence (NICE) guidance suggests that no patients should be given prophylaxis for endocarditis, the European Society of Cardiology recommends that in patients with right-to-left shunt, then prophylaxis should be offered. Patients should be advised on careful skin care (e.g. acne) and antibiotic prophylaxis to prevent local infections that may ‘metastasize’ to the heart or brain.
- *Arrhythmias:* treat in the standard way (➡ Arrhythmias: general approach, p. 58; ➡ Tachyarrhythmias heart rate >120bpm, pp. 60–1; ➡ Treatment options in tachyarrhythmias, p. 62; ➡ Broad complex tachycardia: diagnosis, p. 64; ➡ Monomorphic ventricular tachycardia (MVT), pp. 66–7; ➡ Polymorphic ventricular tachycardia, pp. 68–9; ➡ Ventricular tachycardia: drugs, p. 70; ➡ Narrow complex tachyarrhythmias (SVT), pp. 72–3; ➡ Dosages of selected antiarrhythmics for SVT, p. 75; ➡ Atrial fibrillation: assessment, pp. 76–7; ➡ Atrial fibrillation: management, pp. 78–9; ➡ Atrial fibrillation: rate control, p. 81; ➡ Atrial flutter, p. 82; ➡ Multifocal atrial tachycardia, p. 83; ➡ Accessory pathway tachycardia (AV re-entrant tachycardia), p. 84; ➡ Atrioventricular nodal re-entry tachycardia, p. 85; ➡ Bradyarrhythmias: general approach, pp. 86–7; ➡ Sinus bradycardia or junctional rhythm, p. 88; ➡ Types of atrioventricular conduction block, p. 90).

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Management

Patients can be very complex and must be discussed with their regular cardiologist and/or local congenital adult heart centre.

General measures

- Contact and take advice from the cardiologist normally involved in the patient's care.
- IV lines are potentially very hazardous due to the risk of sepsis and systemic embolization (air and particulate matter). Use an air filter if available. Remove IV cannulae if there are any local signs of thrombophlebitis.
- Avoid sudden changes in circulating volume (e.g. vomiting, diarrhoea, haemorrhage, venesection). Any acute fall in SVR may precipitate intense cyanosis and death, and an acute rise in SVR may abruptly reduce systemic blood flow and cause collapse.
- Monitor for neurological signs and symptoms from cerebral thromboembolism or septic embolism.

Specific measures

- *Haemoptysis*: common. Most episodes are self-limiting and precipitated by infection. Differentiation from PE may be difficult. Try to keep the patient calm, and ensure adequate BP control. Give high-flow O₂ by mask. If there is clinical suspicion of infection (fever, sputum production, leucocytosis, raised CRP, etc.), start broad-spectrum antibiotics. V/Q scan may help in the diagnosis of PE (➡ Pulmonary embolism (PE): assessment, p. 126) but is often equivocal. Avoid aspirin and NSAIDs, as these exacerbate the intrinsic platelet abnormalities. There is anecdotal evidence for the use of low-dose IV heparin, dextran 40 (500mL IV infusion q4–6h), acrid (Arvin®; reduces plasma fibrinogen by cleaving fibrin), or low-dose warfarin therapy for reducing the thrombotic tendency in these patients. Severe pulmonary haemorrhage may respond to aprotinin or tranexamic acid.
- *Breathlessness*: may be due to pulmonary oedema or hypoxia (↑shunt) secondary to chest infection or pulmonary infarction. Do not give large doses of diuretics or nitrates, as this will drop systemic pressures and may precipitate an acute collapse. Compare CXR to previous films to try to assess if there is radiological evidence of pulmonary oedema. The JVP in patients with cyanotic congenital heart disease is typically high and should not be used as a sole marker of heart failure. Overall patients need a higher filling pressure to maintain pulmonary blood flow. Give high-flow O₂ by mask. Start antibiotics if there is a clinical suspicion of infection (see Table 2.1). Give oral diuretics if there is evidence of pulmonary oedema or severe right heart failure. Monitor haematocrit and renal function closely for signs of overdiuresis.
- *Effort syncope*: should prompt a search for arrhythmias, in particular VT (Holter monitor), severe valve disease, or signs of overt heart failure. Treat as appropriate.

- *Chest pain*: may be secondary to PE or infarction (spontaneous thrombosis), pneumonia, IHD, or musculoskeletal causes. It requires careful evaluation with the conventional diagnostic modalities already described.

For a list of congenital defects with survival to adulthood, see Box 1.45. For a list of causes of cyanosis in adults with congenital heart disease, see Box 1.46.

Box 1.45 Congenital defects with survival to adulthood

Common

- Bicuspid aortic valve.
- Coarctation of the aorta.
- Pulmonary stenosis.
- Ostium secundum ASD.
- PDA.
- Coronary or pulmonary AV fistulae.
- Aneurysm of sinus of Valsalva.

Rarer

- Dextrocardia (situs solitus or invertus).
- Congenital CHB.
- Congenitally corrected transposition.
- Ebstein's anomaly.

Congenital defects with good prognosis after surgery

- VSD.
- Fallot's tetralogy.

Box 1.46 Causes of cyanosis in adults with congenital heart disease

- 'Eisenmenger reaction': right-to-left shunt through VSD, ASD, or patent foramen ovale (PFO) with pulmonary hypertension (pulmonary hypertension may be secondary to pulmonary vascular disease, pulmonary artery stenosis or banding, pulmonary valve stenosis, or tricuspid atresia).
- Abnormal connection: transpositions, IVC or SVC to LA, total anomalous pulmonary venous drainage.
- Pulmonary AV fistulae.

Respiratory emergencies

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Acute pneumonia: assessment

Presentation

- Classically cough (productive or non-productive), fever, breathlessness, chest pain, abnormal CXR. There may be prodromal symptoms of coryza, headache, and muscle aches.
- The aetiological agent cannot be predicted from the clinical features (see Box 2.1).
- Immunocompromised patients may present with agitation, fever, tachypnoea, and ↓ routine oximetry readings. CXR abnormalities may be subtle.
- Patients with right-sided endocarditis (e.g. IV drug users) may present with haemoptysis, fever, and patchy consolidation ± cavitation.

Severity assessment

- Severity assessment is the key to deciding the site of care (i.e. home, medical ward, or critical care ward) and guiding general management and antibiotic treatment.
- The 'CURB-65' score may be used as a severity assessment tool (see Boxes 2.2 and 2.3):
 - CURB-65 score ≥ 3 : high risk of mortality; should be admitted and managed as having severe pneumonia.
 - CURB-65 score of 2: ↑ risk of mortality, need short-stay inpatient treatment or hospital-supervised outpatient treatment.
 - CURB-65 score of 0–1: low risk of mortality, may be suitable for home treatment.

Management

General resuscitation and investigations

- Check 'ABC' (airway, breathing, and circulation). Arrange for urgent CXR.
- Secure venous access: if there are signs of dehydration, start IV crystalloids; examine regularly for signs of fluid overload.
- Send bloods: FBC, U&Es, LFTs, CRP.
- Check ABG: correct hypoxia ($P_aO_2 \leq 10\text{kPa}$) with O_2 , at least 35%. If hypoxia fails to correct, despite maximum inspired O_2 , or there is hypercapnia ($P_aCO_2 \geq 6\text{kPa}$), the patient is likely to require ventilation. Patients in type 2 respiratory will require controlled O_2 therapy. Involve ITU early to plan the patient's care.
- Culture blood and sputum.
- Pain relief: paracetamol or an NSAID usually suffice. Morphine may be required; respiratory depression is unlikely to be a problem if P_aCO_2 is low or normal and it may be reversed with naloxone.

Indications for intensive care

- Patients with >2 components of CURB (Confusion, raised Urea, raised Respiratory rate, low BP; see Box 2.2) who do not respond rapidly.
- Persisting hypoxia with $P_aO_2 < 8\text{kPa}$ despite maximal O_2 administration.
- Progressive hypercapnia ($P_aCO_2 \geq 6\text{kPa}$), progressive exhaustion.
- Severe acidosis ($\text{pH} < 7.26$).
- Shock, depressed consciousness.
- Involve ITU early—this may help avoid ventilation as an emergency.

Box 2.1 Causes of acute pneumonia in patients admitted to hospital

Community-acquired

- *Streptococcus pneumoniae* (40%).
- *Haemophilus influenzae* (5%).
- *Staphylococcus aureus* (2%).
- *Moraxella catarrhalis* (2%).
- Gram –ve bacteria/anaerobes (1%).
- Influenza A and B (11%).
- Other viruses (2%).
- Mixed pathogens (14%).
- No organism identified (25%).

Atypicals

- *Mycoplasma* (11%).
- *Legionella pneumophila* (4%).
- *Chlamydia pneumoniae* (13%).
- Other *Chlamydia* spp. (4%).

Hospital-acquired

- All of the above.

Immunocompromised

- All of the above.

Box 2.2 CURB-65 score

CURB-65 score is a 6-point scale (0–5)—one point for each of the following on initial assessment):

- Confusion (defined as Mental Test Score ≤ 8 or new disorientation in time, person, or place).
- Urea >7 mmol/L.
- Respiratory rate (≥ 30 /min).
- Blood pressure, low systolic (<90 mmHg) or diastolic (≤ 60 mmHg).
- Age ≥ 65 years.

Reproduced from *Thorax*, 'Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study', Lim WS, et al. 58: 377–82, copyright 2003, with permission from BMJ Publishing Group Ltd.

Box 2.3 Pneumonia severity, recommended place of management, and mortality

- Low severity (CURB-65 = 0–1): home, mortality $<3\%$.
- Moderate severity (CURB-65 = 2): hospital, mortality 9%.
- High severity (CURB-65 = 3–5): HDU/ITU, mortality 15–40%.

Further reading

British Thoracic Society, Community Acquired Pneumonia in Adults Guideline Group. *Guidelines for the management of community acquired pneumonia in adults: update 2009*. <https://www.brit-thoracic.org.uk/document-library/clinical-information/pneumonia/adult-pneumonia/bts-guidelines-for-the-management-of-community-acquired-pneumonia-in-adults-2009-update/>

Acute pneumonia: investigations

Investigations

All patients should have:

- ABGs (on air and O_2).
- FBC, U&Es, LFTS, ESR, CRP.
- ECG.
- CXR (see Fig. 2.1).
- Blood cultures.
- Sputum culture, Gram stain, ZN stain (if suspicious of TB), cytology.
- Pleural fluid aspiration (if present) for microscopy, culture, and sensitivity (MC&S), protein, and pH.
- *Pneumococcal* antigen: urine, sputum, or blood.
- Serology (acute and convalescent).
- Cold agglutinins (*Mycoplasma* days 7–14).
- Urine for *Legionella* antigen, sputum for *Legionella* culture, and direct immunofluorescence.

Where appropriate, consider:

- Bronchoscopy [$\pm$ bronchoalveolar lavage (BAL)] (if immunocompromised, or if fails to respond to first-line antibiotics and no organism identified).
- Echo (? right heart endocarditis;  Infective endocarditis (IE), pp. 102–3).
- CTPA (to exclude infected pulmonary infarct).
- Transbronchial or open lung biopsy.
- Aspiration of pleural fluid for MC&S.
- Viral titres.

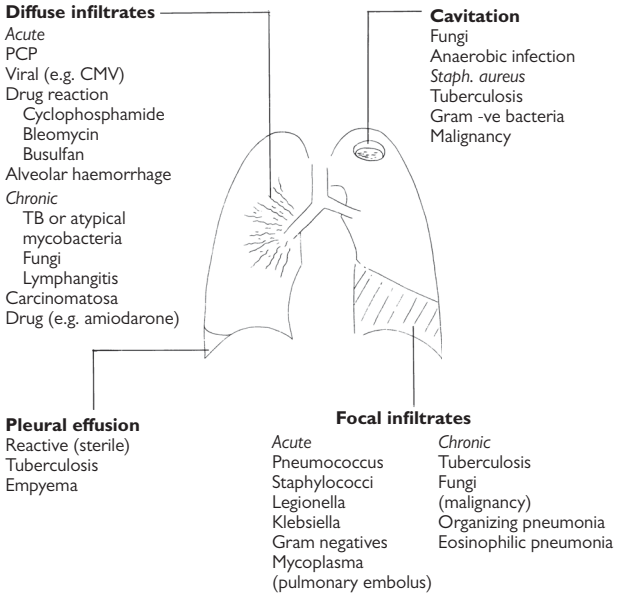


Fig. 2.1 Acute pneumonia: chest investigations.

Acute pneumonia: management

Treatment

- For management key points, see Box 2.4.
- 'Blind' treatment should be started as soon as appropriate cultures have been sent (see Table 2.1). Modify therapy in light of subsequent investigations or positive cultures.
- Start on IV therapy (for at least 48h in patients with high CURB scores); adjust according to clinical condition and response (see Table 2.1).
- All patients should receive appropriate O₂ therapy (aim SpO₂ 94–98%; 88–92% if known COPD/risk of hypercapnic respiratory failure).
- In patients with COPD or asthma, consider treatment with salbutamol (2.5–5mg nebulized q4–6h) to relieve bronchospasm. This may also 'loosen secretions' and improve mucociliary action.
- Continue IV fluids, as necessary, to keep the patient well hydrated.
- Prophylaxis for venous thromboembolism (VTE) with LMWH should be considered for all patients who are not fully mobile.
- Monitor response to therapy with:
 - FBC, CRP.
 - Pulse oximetry or ABGs.
 - CXR at days 3–5 (sooner if deteriorating).
- Total duration of therapy usually 5–7 days (in low-risk patients), up to 10 days (in high-risk patients).
- Follow-up CXR 4–6 weeks after discharge mandatory to exclude an underlying endobronchial lesion.
- Patients should not be discharged if they have >1 of the following features of instability: temperature >37.8°C; pulse rate >100 bpm; RR >24/min; SBP <90mmHg; O₂ saturation <90%; abnormal mental status; and inability to maintain oral intake.

Choice of antibiotics

In severely ill patients, the history may point to a likely pathogen:

- COPD: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*.
- Alcoholism: *S. pneumoniae*, *S. aureus*, *H. influenzae*, *Klebsiella*, TB, anaerobes, Gram –ve bacteria.
- Recent 'flu': *S. aureus*, *S. pneumoniae*, *H. influenzae*.
- Risk of aspiration: anaerobes, Gram –ve bacteria.
- Contact with birds: *Chlamydia psittaci*.
- Haemoptysis: streptococci, *S. aureus*, lung abscess, necrotizing Gram –ve bacteria, invasive aspergillosis.
- Diarrhoea, abdominal pain: *Legionella*.
- Pharyngitis/otitis media: *Mycoplasma*, anaemia/cold agglutinins.
- Risk factors for HIV: *S. pneumoniae*, *H. influenzae*, CMV, *Pneumocystis jiroveci* (*carinii*) pneumonia (PCP), *Cryptococcus*.
- Hospital-acquired: Gram –ve bacteria, *S. aureus*.
- Neutropenia: *Pseudomonas aeruginosa*, Gram –ve bacteria, *Aspergillus*.
- Drug addicts: *S. aureus*, *Candida*.
- Nursing home patients: higher risk of aspiration—anaerobes, Gram –ve bacteria.

'Blind' treatment of pneumonia

- Most patients can be adequately treated with oral antibiotics.
- Consider IV antibiotics if adverse prognostic features present (➡ Acute pneumonia: assessment, p. 172).

In patients with a good history of *penicillin allergy* (anaphylaxis, urticaria). alternatives include erythromycin, clarithromycin, levofloxacin, and moxifloxacin (NB Ciprofloxacin is not very active against *S. pneumoniae*). Alternatives for flucloxacillin include vancomycin, teicoplanin, or rifampicin [consult the *British National Formulary (BNF)* for dosages].

Box 2.4 Management key points: pneumonia

- Correct hypoxia, and assess gas exchange.
- Determine the severity (CURB-65) and best place of care.
- Involve ITU early if ventilatory support likely to be required.
- Send off blood and sputum cultures, and start empirical antibiotic treatment (IV initially for CURB-65 scores of 2 and above).
- Adjust antibiotic treatment in light of the history (predisposing factors) and Gram stain/culture results.
- Monitor for treatment response, and beware of potential complications (parapneumonic effusion, empyema, cavitation, abscess, resistant organisms, underlying disease).

Arrange appropriate follow-up with CXR post-discharge.

Table 2.1 Empirical therapy for pneumonia

Community-acquired pneumonia (CAP)	
Mild (CURB-65: 0–1)	Amoxicillin 500mg tds PO or doxycycline 200mg loading dose, then 100mg daily or clarithromycin 500mg bd
Moderate (CURB-65: 2)	Amoxicillin 500mg–1g tds <i>plus</i> clarithromycin or doxycycline*
Severe (CURB-65: 3–5)	Co-amoxiclav 1.2g tds <i>plus</i> clarithromycin 500mg bd IV or cefuroxime/cefotaxime <i>plus</i> clarithromycin 500mg bd IV
Hospital-acquired pneumonia	Cefotaxime (or ceftazidime) ± metronidazole
Post-influenza pneumonia (<i>S. aureus</i> possible)	Cefuroxime (or amoxicillin + clarithromycin + flucloxacillin)
If MRSA isolated or suspected	Switch flucloxacillin to vancomycin
Aspiration pneumonia	Cefuroxime + metronidazole or benzylpenicillin + gentamicin + metronidazole
Patient with risk factors for HIV and suspicion of PCP	As for CAP + high-dose IV co-trimoxazole

If intolerant of β -lactam or macrolide, use a fluoroquinolone with activity against *S. pneumoniae* (e.g. levofloxacin) or doxycycline (200mg, then 100mg od).

Acute pneumonia: specific situations

Community-acquired pneumonia

- Either *amoxicillin* or *cefuroxime* plus *clarithromycin* to cover atypicals plus *flucloxacillin* if *S. aureus* is suspected.
- *Penicillin allergy*: cephalosporins are usually safe where there is a history of rashes with penicillin. If there is a history of anaphylaxis, consider *clarithromycin* as sole therapy, or if unwell, seek respiratory/microbiological advice.

Aspiration pneumonia

- Risk factors include: seizures, reduced conscious level, stroke, dysphagia, periodontal disease, alcohol dependence, general anaesthesia, and nursing home residents. Always admit.
- Anaerobic bacteria and Gram –ve enteric bacilli may be more common.
- Clinical features include: wheeze and frothy non-purulent sputum (as soon as 2–4h after aspiration), tachypnoea, cyanosis, and respiratory distress.
- Gastric acid destroys alveoli, resulting in ↑capillary permeability and pulmonary oedema. Haemorrhage is common. Severe necrotizing pneumonia may result.
- *Treatment*: *cefuroxime* + *metronidazole* or *amoxicillin* + *metronidazole* + *gentamicin*.

Hospital-acquired pneumonia

- Most likely organisms are enteric Gram –ve bacteria ± anaerobes.
- Patients with diabetes are more susceptible to bacteraemic pneumococcal pneumonia.
- *Treatment*: broad-spectrum cephalosporin (e.g. *cefotaxime* 2g tds IV) and *metronidazole* (500mg IV tds). If intubated for ≥48h, use anti-pseudomonal antibiotic (e.g. *ceftazidime* 2g tds; modify dose in renal failure).

Pneumonia in the immunocompromised

- All 'routine' pathogens are possible; other infections depend on the nature of immunosuppression. TB and atypical mycobacteria are more common.
- Since the introduction of combination antiretroviral treatment, opportunistic infections are less common and pulmonary Kaposi's sarcoma or lymphoma are rarely seen. However, pulmonary opportunistic infection may be the first manifestation of HIV before it is diagnosed, the most common being *Pneumocystis carinii*. Fungal and viral (CMV) pneumonitis may also occur. Desaturation on exercise in the presence of a normal CXR or one with diffuse interstitial shadowing is highly suggestive of PCP.
- Recipients of *organ transplants* have depressed cell-mediated immunity due to anti-rejection immunosuppressive therapy. Additional pathogens to which they are susceptible include PCP, viruses [e.g. CMV, respiratory syncytial virus (RSV), influenza and parainfluenza, adenovirus], and fungi (*Aspergillus* and *Candida* spp.). CXR abnormalities tend not to be specific for the pathogen, and treatment should cover all possible pathogens.
- In general, early bronchoscopy and BAL are indicated for diagnosis; management should be discussed early with the respiratory/ID/microbiology team.

Acute pneumonia: complications

Community-acquired pneumonia that fails to respond

- Review the diagnosis (? PE, pulmonary oedema, pulmonary vasculitis, alveolar haemorrhage, cavitation, organizing pneumonia, eosinophilic pneumonia, bronchiectasis).
- Repeat CXR, and arrange for CT chest to look for cavitation or empyema. Refer to the respiratory team. Repeat culture of relevant specimens (e.g. sputum, blood). Consider possible resistant organism or underlying disease, e.g. bronchial carcinoma.
- Consider bronchoscopy to exclude TB, PCP, or an obstructing lesion.
- Review antibiotic dosages, and intensify (e.g. inadequate oral clarithromycin for *Mycoplasma pneumoniae*).

Parapneumonic pleural effusion or empyema

- Parapneumonic pleural effusions develop in up to 50% of patients with bacterial pneumonia admitted to hospital.
- Image-guided diagnostic tap should be performed on all parapneumonic effusions to exclude an empyema. Send pleural fluid for MC&S, urgent Gram stain, and pH analysis.
- Empyema (visibly cloudy fluid, pus, or organisms on Gram stain) or a complicated parapneumonic effusion (visibly clear fluid with pH <7.2) should be removed with pleural space drainage under US guidance. Discuss with respiratory physicians.
- US may help look at the level of the effusion and demonstrate loculation with an empyema.
- If an empyema fails to resolve with pleural space drainage, arrange chest CT and discuss with cardiothoracic surgeons (➡ Indications for specialist referral, p. 221).

Cavitation or abscess

Any severe pneumonia may cavitate, but particularly *S. aureus*, *Klebsiella* spp., TB, aspiration pneumonia, bronchial obstruction (foreign body, tumour), or PEs (thrombus or septic emboli, e.g. from DVT with superadded infection or tricuspid endocarditis; ➡ Right-sided endocarditis, p. 112).

Treatment

- Seek advice from the respiratory team. Most respond to appropriate antibiotics but may require a more prolonged course. Surgical drainage or CT-guided percutaneous aspiration may be necessary.
- 'Blind' treatment: cefuroxime 1.5g tds IV (or cefotaxime 2g tds IV) + flucloxacillin 1–2g qds IV + gentamicin loading dose (100–120mg IV), then 6–7mg/kg od (according to renal function and levels) ± metronidazole 500mg IV tds.
- Long-term antibiotics (4–6 weeks) likely to be required.

Other complications

- Respiratory failure (➡ Respiratory failure: assessment, pp. 198–9).
- Rhabdomyolysis (➡ Rhabdomyolysis, pp. 306–7).
- DIC (especially *Legionella*) (➡ Disseminated intravascular coagulation, p. 633).

Mycoplasma pneumonia

- Disease of young adults. Low-grade fever, dry cough, headache, and myalgia. Erythema multiforme may be seen in ~25%; ~5% have meningoencephalitis.
- Epidemics occur every 4 years in the UK.
- WCC is often normal; ESR is high; specific immunoglobulin M (IgM) is seen early, then levels decline. ~50% develop cold agglutinins (also seen in measles, EBV) which may cause haemolysis. CXR may show reticulonodular shadowing (lower lobe > upper lobe), which may take over 6 weeks to resolve (unlike bacterial pneumonia).
- Treatment is with erythromycin 500mg qds PO/IV, clarithromycin 500mg bd PO/IV, or tetracycline 500mg qds PO/IV.

Legionella pneumonia

- Illness of middle-aged men; more severe in smokers. Incubation 2–10 days, followed by high fever, rigors, headache, myalgia, dry cough, progressive respiratory distress, and confusion. Abdominal pain, diarrhoea, nausea and vomiting, and palpable hepatomegaly are seen in ~30%. Complications include pericarditis ($\pm$ effusion), encephalopathy [cerebrospinal fluid (CSF) is usually normal], and rarely renal failure.
- Moderate leucocytosis ($\leq 20 \times 10^9/L$, neutrophilia, lymphopenia), hyponatraemia, deranged LFTs, proteinuria, haematuria, and myoglobinuria. Diagnosis: rise in specific IgM and immunoglobulin G (IgG) titres (urine, blood, sputum).
- Worth sending urine for urinary *Legionella* antigen.
- CXR may show anything from diffuse patchy infiltrates to lobar or segmental changes and usually deteriorates in spite of treatment. Pleural effusions are seen in ~50%.
- Treatment is with clarithromycin 500mg bd PO/IV. Continue therapy for 14–21 days. Add rifampicin (600mg bd PO/IV) if symptoms do not settle within 72h.
- Pontiac fever is a self-limiting (2–5 days), acute, non-pneumonic *Legionella* infection with high fever, rigors, myalgia, headache, and tracheobronchitis.

Viral pneumonia

Clinical features resemble *Mycoplasma pneumoniae* (➡ *Mycoplasma pneumoniae*, p. 180). Diagnosis is by a 4-fold increase in specific antibody titres.

CMV

Most common viral infection in AIDS and following solid organ or bone marrow transplantation (BMT), presenting as fever, dry cough, and progressive respiratory distress with hypoxia and bilateral crackles. CXR shows diffuse infiltrates; a miliary pattern is associated with rapid progression and poor outcome, whereas an interstitial pattern has a better prognosis (see Fig. 2.1). Treat with *ganciclovir* 5mg/kg IV q12h for 2–3 weeks.

Coxsackie and echovirus

Titres often rise in ‘epidemic pleurodynia’ (Bornholm’s disease), a self-limiting illness with chest pain, exacerbated by coughing and deep breathing, myalgia, and muscle tenderness. Treatment: analgesia (paracetamol, NSAIDs).

Varicella pneumonia

More common in smokers and immunosuppressed patients. All patients with varicella pneumonitis should be treated with *aciclovir* 10mg/kg IV 8-hourly.

Chlamydia pneumoniae

- *C. pneumoniae* presents in older adults with headaches and longer duration of symptoms before hospital admission. Extra-pulmonary manifestations may include meningoencephalitis, Guillain–Barré syndrome (GBS), arthritis, and myocarditis.
- Treatment: *erythromycin* 500mg qds PO/IV, *clarithromycin* 500mg bd PO/IV, or *tetracycline* 500mg qds PO/IV.

Psittacosis

- *C. psittaci* produces fever, cough, myalgia, and, in severe cases, delirium (psittacosis). Complications include pericarditis, myocarditis, and hepatosplenomegaly. Diagnosis is by serology.
- Acquired from birds and animals (so may be a clue in the history), but human-to-human spread may occur.
- Treat with tetracycline 500mg PO qds for 2–3 weeks.

In summary, the likely aetiological agent causing CAP cannot be accurately predicted from the clinical features. However, some patient groups/signs and symptoms tend to be more commonly associated with certain pathogens:

- *S. pneumoniae*: increasing age, comorbidity, high fever, pleuritic chest pain.
- Bacteraemic *S. pneumoniae*: ♀, excess alcohol, diabetes mellitus (DM), COPD, dry cough.
- *Legionella*: younger patient, smoker, absence of comorbidity, diarrhoea, neurological symptoms, multisystem involvement.
- *Mycoplasma*: younger patient, prior antibiotics, less multisystem involvement.
- *C. pneumoniae*: longer duration of symptoms prehospital admission and headache.
- *Coxiella burnetii*: ♂, dry cough, high fever.

Miscellaneous conditions

Hypersensitivity pneumonitis (extrinsic allergic alveolitis)

May mimic viral pneumonia and present as breathlessness, dry cough, myalgia, and fever, with neutrophilia (eosinophils usually normal acutely) and patchy radiographic changes. There is usually a history of exposure to the allergen, and serum precipitins are detectable. BAL shows predominance of mast cells and lymphocytes. Treatment is with steroids.

Pulmonary eosinophilia

This is a heterogeneous group of disorders characterized by eosinophilic pulmonary infiltrates, producing respiratory symptoms, CXR shadowing, and blood and sputum eosinophilia. The cause may be unknown, as in cryptogenic eosinophilic pneumonia, or it may be due to drugs (e.g. nitrofurantoin, phenytoin, and ampicillin), helminth infections (e.g. *Ascaris lumbricoides*, hookworms, *Strongyloides stercoralis*), tropical pulmonary eosinophilia (lymphatic filarial infection), or small-vessel systemic vasculitis (Churg–Strauss).

Allergic bronchopulmonary aspergillosis

This is a hypersensitivity reaction of airways colonized by *Aspergillus* spp. producing pulmonary eosinophilia. It typically occurs in asthmatics with repeated episodes of bronchial obstruction, inflammation, and mucus impaction, resulting in bronchiectasis and upper lobe fibrosis. Such patients are usually *Aspergillus* skin-prick test [immunoglobulin E (IgE)] and serum precipitins (IgG) positive. Treatment depends on the underlying condition.

Cryptogenic organizing pneumonia

May present with fever, malaise, cough, breathlessness, and pulmonary shadows on CXR. Characteristically, infiltrates in different lobes over different time courses, or pneumonia unresponsive to antibiotics. Excessive proliferation of granulation tissue within small airways and alveoli, cryptogenic organizing pneumonia (COP) is the idiopathic form of bronchiolitis obliterans organizing pneumonia (BOOP). Organizing pneumonia can also be associated with collagen vascular diseases (RA, lupus, dermatomyositis), chronic infection (*Legionella*, CMV, *Mycoplasma*), and drugs (amiodarone, bleomycin). Treatment is with steroids.

Alveolar haemorrhage

Intrapulmonary haemorrhage may present with cough, fever, and breathlessness. Haemoptysis may be absent in 30%. The CXR may show diffuse alveolar opacities. BAL shows predominantly RBCs. Causes include systemic vasculitis (e.g. Wegener's granulomatosis, microscopic polyangiitis), collagen vascular diseases (e.g. SLE), Goodpasture's syndrome, ARDS, and idiopathic pulmonary hemosiderosis. Treatment depends on the cause.

Bronchoalveolar cell carcinoma

May mimic an acute pneumonia radiologically, although the typical symptoms of pneumonia are usually not present, unless there is superadded infection. Diagnosis is made by lung biopsy.

Acute asthma: assessment

Presentation

- The classical triad is *wheeze ± chest tightness, breathlessness, and cough*. Symptoms are often worse at night and first thing in the morning. Acute attacks may build up *over minutes, hours, or days*, and the patients may deteriorate very rapidly and present as respiratory or cardiorespiratory arrest.
- Factors increasing the risk of severe life-threatening asthma include: previous ventilation, hospital admission for asthma in the last year, heavy rescue medication use, >3 classes of asthma medication, repeated attendances at A&E for asthma care, and brittle asthma.

Precipitants

- No clear precipitating cause can be identified in over 30% of patients.
- Exposure to known allergen or irritant (e.g. pollens, animals, dusts, cigarette smoke).
- Upper respiratory tract infection (URTI) (commonly viral).
- Lower respiratory tract infection (LRTI)—viral or bacterial.
- Neglect or poor compliance with regular inhaled or oral steroids.
- Emotional stress.
- Cold air or exercise-induced asthma.

Markers of severity

- For assessment of the severity of asthma, see Box 2.5.
- The severity of an attack may be easily underestimated. Assess:
 - The degree of airflow obstruction.
 - The effect of ↑work of breathing on the patient.
 - The extent of V/Q mismatch.
 - For any evidence of ventilatory failure.

[Patients with marked ‘morning dips’ in the peak expiratory flow (PEF) are at risk of sudden severe attacks.]

Investigations

- ABG: patients with $\text{SpO}_2 < 92\%$ on air or with other features of severe asthma require ABG measurement. Hypoxaemia on room air is almost invariable. In attempting to maintain alveolar ventilation initially, there is hypocapnia and respiratory alkalosis. $\uparrow P_a\text{CO}_2$ suggests incipient respiratory failure due to exhaustion; contact ITU immediately. Poorly controlled asthma over several days may be recognized by a mild ‘non-anion gap’ acidosis (serum bicarbonate 20–24mmol/L). Lactic acidosis is seen with severe asthma.
- *Pulse oximetry*: continuous oximetry is essential; aim for 94–98%.
- *CXR*: to exclude pneumothorax and diagnose any parenchymal infection.
- *ECG*: usually normal; in severe asthmatics, signs of right heart strain may be present.
- *FBC, U&Es, CRP*: assess for signs of infection and eosinophilia; K^+ may be lowered by high doses of β -agonists.

Box 2.5 Assessment of severity of acute asthma

A. Near-fatal asthma

- Raised $P_a\text{CO}_2$ or immediate requirement for ventilation with raised inflation pressures.

B. Life-threatening asthma

1. Severe airways obstruction

- PEF <33% best or predicted.
- Soft breath sounds or 'silent chest'.
- Feeble respiratory effort.

2. Increased work of breathing and haemodynamic stress

- Exhaustion.
- Hypotension (SBP <100mmHg).
- Bradycardia or arrhythmia.

3. V/Q mismatch

- Cyanosis.
- Hypoxia (SpO_2 <92% and/or $P_a\text{O}_2$ <8kPa).
- Normal $P_a\text{CO}_2$ (4.6–6.0kPa).

4. Ventilatory failure

- Rising $P_a\text{CO}_2$ suggests 'near-fatal' asthma.
- Confusion or coma.

C. Acute severe asthma

- PEF $\geq$ 33–50% best or predicted.
- RR $\geq$ 25/min.
- Tachycardia: HR $\geq$ 110bpm.
- Inability to complete sentences in one breath.

D. Moderate acute asthma

- Increasing symptoms.
- PEF >50–75% best or predicted.
- No features of acute severe asthma.

Admission is mandatory if *any* of the markers of severe, life-threatening, or near-fatal asthma are present.

Source: data from SIGN 153: *British guideline on the management of asthma* (2016). <https://www.brit-thoracic.org.uk/standards-of-care/guidelines/btsgn-british-guideline-on-the-management-of-asthma>

Acute severe asthma: immediate therapy

Priorities

1. Treat hypoxia.
2. Treat bronchospasm and inflammation.
3. Assess the need for intensive care.
4. Treat any underlying cause, if present (e.g. infection, pneumothorax).
 - Patients may deteriorate rapidly and should not be left unattended.
 - *Remain calm*: reassurance is important in reducing the patient's anxiety which may further increase the respiratory effort (see Box 2.6).

Severe or life-threatening attack

(See Box 2.7.)

1. Initial treatment

- Sit the patient up in bed.
- O_2 : the highest percentage available, ideally at least 60% or 15L/min with a high-flow mask. CO_2 retention is not a problem in asthmatic patients. Maintain O_2 saturations $>92\%$.
- *Nebulized bronchodilators*: give nebulized salbutamol 2.5mg or terbutaline 10mg, administered via O_2 , and repeat up to every 15–30min if required. Consider continuous nebulization of salbutamol 5–10mg/h if inadequate response to initial treatment.
- Add *ipratropium bromide* 0.5mg 4- to 6-hourly if initial response to β_2 agonists is poor.
- Obtain IV access.
- Start *steroids*: if able to take tablets, prednisolone 40mg PO; if not, 200mg of hydrocortisone IV (steroids should still be used in pregnant women, as the risk of fetal anoxia from asthma is high). Continue prednisolone 40mg od PO.
- *Antibiotics* should be given if there is evidence of chest infection (purulent sputum, abnormal CXR, raised WCC, fever). Yellow sputum may just be due to eosinophils, and a raised WCC may be due to steroids. See 🔄 Acute pneumonia: management, pp. 176–7 for choice of antibiotics. Routine prescription of antibiotics is not recommended for patients with acute asthma if no evidence of an infective precipitant.
- *Adequate hydration* is essential and may help prevent mucus plugging. Ensure an intake (IV or PO) of 2–3L/day, taking care to avoid overload. Supplement K^+ , as required.

2. Monitoring progress

- Pre- and post-nebulizer peak flows.
- Repeated ABGs 1- to 2-hourly or according to response, especially if $SpO_2 < 93\%$. Remember ABGs are painful—the British Thoracic Society (BTS) guidelines state that a local anaesthetic should be used. Alternatively, consider an arterial line if frequent sampling.

3. If response to treatment not brisk or if the patient's condition is deteriorating

- Continue O_2 and nebulized β_2 agonist every 15min.
- Give a single dose of IV magnesium sulfate (see Box 2.8).
- Summon anaesthetic help.
- Consider starting an IV *aminophylline infusion* (see Box 2.8).
- Consider starting an IV *salbutamol infusion* (see Box 2.8).

Box 2.6 Management key points: acute asthma

- O_2 .
- Nebulized salbutamol and ipratropium bromide.
- Oral prednisolone.
- Monitor peak expiratory flow rate (PEFR) and ABG.
- If no improvement: IV magnesium sulfate.
- Summon anaesthetic help if the patient is not improving or is getting tired (P_aCO_2 increasing).
- Consider IV aminophylline infusion or IV salbutamol (with anaesthetic support).
- Monitor serum K^+ daily, and supplement as necessary.
- Treat any underlying cause (e.g. infection, pneumothorax). Give antibiotics if there is evidence of chest infection (purulent sputum, abnormal CXR, raised WCC, fever).

Box 2.7 Indications for admission to intensive care unit

- Hypoxia [$P_aO_2 < 8kPa$ (60mmHg) despite fraction of inspired oxygen (FiO_2) of 60%].
- Rising P_aCO_2 or $P_aCO_2 > 6kPa$ (45mmHg).
- Exhaustion, drowsiness, or coma.
- Respiratory arrest.
- Failure to improve despite adequate therapy.

Box 2.8 Intravenous bronchodilators for asthma*Magnesium sulfate*

- 1.2–2g if infused over 20min.
- Give as a single dose only. Repeated doses may lead to hypermagnesaemia with muscle weakness and respiratory failure.

Salbutamol

- *Loading dose:* 100–300 micrograms over 10min.
- *Maintenance infusion:* 5–20 micrograms/min (5mg in 500mL of saline at 1–3mL/min).
- *Side effects:* tremor, tachycardia, hypokalaemia, hyperglycaemia common. Lactic acidosis may occur and responds within hours to reduction in salbutamol infusion rate.

Aminophylline

- *Loading dose:* 250mg (4–5mg/kg) IV over 20min.
- *Maintenance infusion:* 0.5–0.7mg/kg/h (250mg in 1L of normal saline at 2–4mL/kg/h).
- Do not give the loading dose if the patient is on oral theophyllines, without checking a serum level.
- Halve the dose in patients with cirrhosis or CCF, or in those receiving erythromycin, cimetidine, or ciprofloxacin. Monitor levels every 24h (aim for levels of 10–20mg/L).

Acute severe asthma: further management

- *Cautious CPAP* may help reduce the work of breathing in patients with respiratory muscle fatigue but may not increase the functional residual capacity further. Involve ITU early, so as not to delay invasive ventilation.
- *Ketamine* (a dissociative anaesthetic agent) may be useful in ventilated patients (1–3mg/min), probably by increasing circulating catecholamines by blocking uptake into adrenergic nerve endings.
- *Inhalational anaesthetic agents* (e.g. halothane, enflurane, isoflurane) have been reported to improve bronchospasm and may be useful when initiating ventilation.
- *Mechanical ventilation* may be lifesaving but has a high risk of complications and an overall mortality of ~13%. Barotrauma is seen in ~14% (e.g. pneumothorax, pneumomediastinum, or subcutaneous emphysema), and hypotension in ~38% (usually a combination of ↑intrathoracic pressure, intravascular fluid depletion due to dehydration, and dilating effect of anaesthetic agents). Seek expert advice from your intensive care physician for the practical management of ventilation of the asthmatic patient.

General principles

- Adequate humidification and warming of inspired gases.
- Low-frequency ventilation (6–10 breaths/min).
- Low tidal volumes (6–10mL/kg).
- Long expiratory phase of the cycle (I:E ratio 1:3 or longer).
- Minimize airway pressures (aim for <50cmH₂O, normal <25cmH₂O).
- Maintain $P_aO_2 > 8.0$ kPa; allow P_aCO_2 to rise, provided pH > 7.2.
- Adequate sedation and paralysis to overcome respiratory drive.
- Avoid opiates and atracurium (may release histamine).
- Consider benzodiazepine, ketamine, vecuronium, isoflurane, etc.

Ongoing therapy

- Once improvement established, continue nebulized β_2 -agonist, reducing this to 4-hourly and PRN after 24–48h.
- PEFR should be measured before and after each nebulizer.
- Maintain O₂ saturations 94–98%.
- Continue nebulized ipratropium bromide 6-hourly until the condition is improving.
- Continue steroids, 40mg od prednisolone PO, for 10–14 days.
- Monitor IV aminophylline levels every 24h.
- Monitor serum K⁺ daily while unwell, and supplement as necessary.
- Checking inhaler technique predischage is essential.
- Discharge criteria (see Box 2.9).

Box 2.9 Discharge after hospital admission

- The PEF should be $\geq 75\%$ of best, without significant morning dipping (diurnal variability $\leq 25\%$) and with no nocturnal symptoms.
- The patient should be established on inhalers, with no requirement for nebulizers for 24–48h prior to discharge. Ensure inhaler technique checked.
- Discharge drugs:
 - Prednisolone PO $\geq 30\text{mg}$ od for 1–3 weeks (plan gradual dose reduction if treatment >14 days).
 - Inhaled corticosteroids at high dose (usually 1000–1500 micrograms of beclometasone via spacer or equivalent).
 - Restart inhaled long-acting β_2 -agonists if prescribed prior to admission.
 - Inhaled PRN β_2 -agonist.
 - Oral theophyllines if required (confirm drug levels before discharge).
- Provide a written personalized action plan. The ‘Be in Control’ asthma action plan from Asthma UK can be downloaded directly from their website at  <https://www.asthma.org.uk/control>.
- Provide a PEF meter and chart, and arrange follow-up with the general practitioner (GP) or practice nurse (within 2 days) and chest clinic (within 1 month).
- Assess individual risk factors/precipitants.

Mild to moderate asthmatic attacks

Mild asthmatic attack

No severe features, PEF $\geq 75\%$ of predicted (or of best when well).

- Administer the patient's usual bronchodilator (e.g. two puffs of salbutamol by metered-dose inhaler).
- Observe for 60min. If PEF remains $\geq 75\%$ of predicted value, then discharge.
- Ensure the patient is on at least 1000 micrograms of inhaled beclometasone or equivalent per day.
- Advise the patient to get early GP follow-up, monitor PEF, and return to hospital early if the asthma deteriorates.

Moderate asthmatic attack

No acute severe features, PEF 51–75% of predicted (or of best when well).

- Administer nebulized β -agonist (salbutamol 5mg or terbutaline 10mg) and oral prednisolone 30–60mg.
- Reassess after 30min. If worse or PEF $\leq 50\%$ of predicted, then admit and assess as for severe asthma.
- If PEF 51–75% predicted, then repeat nebulizer and observe for a further 60min.
- The patient may be discharged from A&E if stable after 1–2 nebulizers and PEFR $\geq 75\%$.
- Discharge on:
 - Oral prednisolone (usual dose 30–40mg od for at least 5 days).
 - Inhaled corticosteroid (≥ 1000 micrograms/day of inhaled beclometasone).
 - Inhaled β -agonist.
- Advise the patient to seek GP follow-up within 48h and to return early to A&E if there is any deterioration.
- Consider referral to chest clinic.

Sending people home from A&E

- Mild to moderate exacerbations may be fit to be discharged from A&E.
- If there are any features of acute severe asthma (see Box 2.4), then admission is mandatory.
- A history of brittle asthma or previous attacks requiring mechanical ventilation is always a requirement for admission.

Acute exacerbation of chronic obstructive pulmonary disease: assessment

Presentation

- Deterioration of pre-existing symptoms of exertional breathlessness, cough (sometimes with daily sputum production), and wheeze (unrelieved or only partially relieved by inhaled bronchodilators).
- Respiratory failure (➡ Respiratory failure: assessment, pp. 198–9): may be type 1 (normal $P_a\text{CO}_2$, low $P_a\text{O}_2$) or type 2 (high $P_a\text{CO}_2$, low $P_a\text{O}_2$, reflecting severe bronchospasm and/or alveolar hypoventilation).
- Positive smoking history (if not, then late-onset asthma is likely or the rarer diagnosis of $\alpha 1$ -antitrypsin deficiency should be considered).
- Confusion/impaired consciousness (exhaustion, CO_2 retention).

Causes

- Infective exacerbation (no new CXR changes): typically *H. influenzae*, *S. pneumoniae*, *Moraxella catarrhalis*. Commonly viral.
- CAP (new CXR changes) (see Fig. 2.1).
- Exposure to known allergen: COPD may coexist with allergic asthma.
- Pneumothorax (➡ Pneumothorax: assessment, pp. 210–11): differentiate from large bullae.
- Expansion of large bullae.
- Sputum retention with lobar or segmental collapse (atelectasis): pneumonia, excessive sedation or opioid analgesia (trauma, post-surgery), impaired consciousness.
- Confounding or contributing factors: myocardial ischaemia, pulmonary oedema, cor pulmonale, PE.

Investigations

All patients should have:

- U&Es: look for dehydration and renal failure. Monitor K^+ .
- FBC: look for leucocytosis or anaemia (chronic respiratory failure may produce secondary polycythaemia).
- Pulse oximetry and ABGs: to assess the degree of respiratory failure and pH, and to guide appropriate O_2 treatment.
- Septic screen: sputum should be sent for culture. Blood cultures if febrile or CXR changes suggest pneumonia.
- CXR: focal changes suggest pneumonia (➡ Acute pneumonia: investigations, p. 174).
- ECG: myocardial ischaemia or arrhythmia.

Assessment of severity

- History: assess the severity of COPD when stable, and compare with current exacerbation. Ask about symptoms and functional capacity when well (distance walked on flat, stairs climbed, frequency of exacerbations, previous admissions, ? ever ventilated). Assess the level of usual treatment (regular nebulized bronchodilators or oral steroids, home O_2) and concurrent illnesses (IHD, renal impairment). Any previous documentation [pulmonary function tests (PFTs), ABGs].

- *Examination:* assess for severity of respiratory distress (RR >25/min, use of accessory muscles, or paradoxical chest wall movements), hypoxia (cyanosis), hypercapnia (CO₂ retention flap, confusion), and cor pulmonale (peripheral oedema) (see Box 2.10).

Box 2.10 Criteria for hospital admission

- Marked increase in symptoms.
- Baseline of severe COPD.
- New physical signs, e.g. cyanosis, peripheral oedema.
- Failure to respond to initial management at home.
- Significant comorbidities.
- Diagnostic uncertainty.
- Age >70 years.
- Insufficient home support.

Acute exacerbation of COPD: management

(See Box 2.11.)

Treat hypoxia and respiratory failure

- The distinction between 'pink puffers' (breathless to maintain P_aO_2 and so keep P_aCO_2 down) and 'blue bloaters' (lose breathless drive to maintain P_aO_2 and so P_aCO_2 rises) is unhelpful, as most patients have features of both.
- *Commence O_2 therapy:* uncontrolled O_2 therapy may worsen CO_2 retention in some patients. While awaiting ABGs, give controlled 24–28% O_2 via a Venturi mask. Nasal cannulae give unreliable inspired O_2 concentration and may be dangerous. Once ABG results available, adjust FiO_2 accordingly.
- *ABGs:*
 - If the patient is not retaining CO_2 ($P_aCO_2 < 6kPa$) and is hypoxic ($P_aO_2 < 10kPa$), then give O_2 28–40%. Repeat ABGs 30min later (sooner if conscious level deteriorates) to ensure correction of hypoxia and exclude rising P_aCO_2 . Aim to maintain O_2 saturations 88–92%.
 - If CO_2 retention is present, then use 24–28% O_2 and consider ventilatory support. *Non-invasive ventilation (NIV)* is the first-line treatment of choice for COPD exacerbations with type 2 respiratory failure in patients who fail to respond to initial therapy. It allows the administration of higher O_2 concentrations without an uncontrolled rise in P_aCO_2 . NIV reduces the need for intubation, decreases mortality and hospital stay, and should be considered in all patients with COPD exacerbations with $P_aCO_2 \geq 6.0kPa$ and $pH \leq 7.35$ who have failed to respond to initial bronchodilator therapy.
- *Mechanical ventilation:* this should be considered in patients unlikely or unable to tolerate NIV (➡ Mechanical ventilation, p. 828).
- *Respiratory stimulants:* these have generally been superseded by NIV. However, where NIV is not available or has not been successful and mechanical ventilation is not considered appropriate, a trial of doxapram may be worthwhile. It is not beneficial in type 2 respiratory failure due to poor respiratory effort.

Treat bronchospasm and obstruction

- *Nebulized β -agonists* (salbutamol 2.5mg or terbutaline 10mg q4h and PRN) via O_2 or air if CO_2 retention. (If the patient is very hypoxic, give 2L/min O_2 via nasal cannulae while nebulizer in progress.)
- Patients with COPD may have relatively fixed bronchospasm, but where the patient is very unwell, then consider IV aminophylline and/or IV β -agonists, as for severe asthma (see Box 2.5).
- Include nebulized ipratropium bromide 500 micrograms 6-hourly. This tends to be more effective in patients with COPD than in those with asthma.
- Give *steroids*: 30mg prednisolone PO for 7–10 days; there is no advantage in prolonging therapy.
- Urgent physiotherapy may help clear bronchial secretions.

Box 2.11 Management key points: acute exacerbation of COPD

- O_2 : initially 24–28% O_2 via a Venturi mask (adjust FiO_2 when ABG results available).
- Nebulized salbutamol, ipratropium bromide.
- Oral prednisolone.
- Treat cause of exacerbation, e.g. infective exacerbation or pneumothorax.
- Urgent physiotherapy may help clear bronchial secretions.
- Consider NIV in type 2 respiratory failure patients who fail to respond to initial therapy. Mechanical ventilation should be considered in patients unable/unlikely to tolerate NIV.

Acute exacerbation of COPD

Mechanical ventilation

- COPD per se is not a contraindication to ventilation in appropriately selected patients. Ventilation should be considered where respiratory failure is present ($P_aO_2 \leq 7.3\text{kPa}$), regardless of CO_2 levels, and in those patients who have failed to respond to first-line treatment (including NIV) or who are very severely unwell and unlikely to respond to any other intervention.
- Discuss with a senior colleague or ITU staff prior to intubation.

In favour of a good outcome from ventilation

- Acute respiratory failure (normal bicarbonate, acute history).
- Relatively young patient.
- Obvious remediable cause (e.g. pneumonia).
- Good recent exercise tolerance and quality of life.
- Not previously known to retain CO_2 when well.

Against a good outcome from ventilation

- Elderly.
- Other comorbid conditions (e.g. IHD, renal failure).
- Previous difficulty weaning from ventilator.
- On maximal therapy at home (home nebulizer, long-term O_2 therapy).
- Poor quality of life or poor exercise tolerance.

Management of gas exchange during ventilation

- Patients who are chronically hypoxic or CO_2 retainers will tolerate poor blood gases better than those patients with other causes of respiratory failure.
- When ventilating patients with COPD, achieving a 'normal' P_aCO_2 and P_aO_2 may not be appropriate. Those who are chronically hypoxic or who chronically retain CO_2 (as evidenced by previous abnormal gases or a raised bicarbonate with a normal or near-normal pH) are unlikely to breath spontaneously or wean from the ventilator, unless their blood gases are allowed to mirror what is probably their chronic state. Thus, a patient with chronic type 2 respiratory failure may need a P_aCO_2 of $6\text{--}7.5\text{kPa} \pm$ mild hypoxia, even on the ventilator, to achieve successful weaning.

Treat the cause of exacerbation

Infective exacerbation

- Suggested by purulent sputum or an increase in sputum production.
- For lobar consolidation or bronchial pneumonia, follow guidelines described under  Acute pneumonia: management, pp. 176–7 and  Acute pneumonia: specific situations, p. 178. Otherwise treat with amoxicillin 500mg–1g tds or doxycycline 200mg loading dose, then 100mg daily PO; if unwell or failure to respond, treat with cefuroxime 750mg tds IV for improved cover of resistant *Haemophilus* spp.
- Follow local protocols.

Pneumothorax

Unless very small, consider aspiration $\pm$ drain (➡ Pneumothorax: assessment, pp. 210–11).

Pulmonary oedema

See ➡ Pulmonary oedema: assessment, pp. 92–3.

Pulmonary embolism

See ➡ Pulmonary embolism (PE): assessment, p. 126.

Respiratory failure: assessment

Respiratory failure is present when gas exchange becomes significantly impaired. Clinically, it is not possible to predict the P_aO_2 or P_aCO_2 , and so this diagnosis relies on ABG analysis. There are two types:

- Type 1: hypoxia $P_aO_2 \leq 8\text{kPa}$ on air or O_2 with normal or low P_aCO_2 (i.e. mainly V/Q mismatch).
- Type 2: hypoxia $P_aO_2 \leq 8\text{kPa}$ on air or O_2 with raised P_aCO_2 ($>6\text{kPa}$) (i.e. predominantly alveolar hypoventilation).

In practice, both types may coexist.

Presentation

(See Box 2.12.)

- *Shortness of breath* is the most common presentation. Ask about the speed of onset (sudden onset may suggest pneumothorax, PE, or cardiac failure).
- Respiratory failure may present without dyspnoea, particularly exacerbations of COPD with hypoventilation and non-respiratory causes such as GBS (➡ Guillain-Barré syndrome, pp. 452–3) or drug overdose. Neuromuscular respiratory failure is discussed under ➡ Neuromuscular respiratory failure: assessment, pp. 440–1.
- *Confusion* may be the sole presentation in the elderly.

The *history* may point to the cause of respiratory failure:

- History of asthma/chronic bronchitis and smoking.
- History of other chronic lung disease (e.g. fibrosing alveolitis, sarcoidosis).
- Sputum production and fevers (pneumonia).
- Swollen legs due to the development of cor pulmonale or hypoxic/hypercapnic renal fluid retention in patients with chronic lung disease.
- Haemoptysis (pneumonia, PE).
- Cardiac history, including palpitations and/or chest pain.
- Drug and/or overdose history.
- Neurological symptoms, including painful legs and paraesthesiae (GBS).
- Allergies.

Try to assess the functional capacity when well, e.g. distance walked on flat, stairs climbed without stopping, frequency of attacks, previous admissions, ever ventilated, concurrent illnesses (heart disease, renal impairment, liver impairment), etc.

Physical examination

- Listen to the breathing: stridor (upper airway obstruction), wheeze (localized or generalized airflow limitation secondary to asthma, COPD, pulmonary oedema), coarse crackles (due to consolidation of fluid), fine crackles (due to fibrotic change), bronchial breathing (indicates consolidation or collapse but may also occur with fibrosis or above a pleural effusion).
- Look for cyanosis, signs of pneumothorax (hyperresonance, reduced breath sounds), or pleural effusion (stony dull, reduced breath sounds).

- Palpate the upper chest and neck for crepitus (pneumothorax or pneumomediastinum).
- Check for signs of DVT (swollen hot leg $\pm$ pain; ➡ Deep vein thrombosis (DVT): assessment, pp. 122–3).

Box 2.12 Causes of respiratory failure

Common

- Acute asthma (➡ Acute asthma: assessment, p. 184).
- Exacerbation of COPD (➡ Acute exacerbation of COPD: management, p. 194).
- Pneumonia (➡ Acute pneumonia: assessment, p. 172).
- Pulmonary oedema (➡ Pulmonary oedema: assessment, p. 92–3).
- PE (➡ Pulmonary embolism (PE): assessment, p. 126).
- Infection complicating kyphoscoliosis or other chronic lung disease.
- Pleural effusion (➡ Pleural effusions, p. 220–1).
- Pneumothorax (➡ Pneumothorax: assessment, p. 210–11).
- ARDS/acute lung injury (ALI) (➡ Adult respiratory distress syndrome 1, p. 204).
- Respiratory depression.
- Drugs, e.g. opiates.

Rarer

- Lung collapse/atelectasis (tumour, foreign body, sputum plug, infection).
- Acute respiratory muscle weakness: GBS (➡ Guillain–Barré syndrome, p. 452–3), myasthenia gravis (➡ Myasthenic crises, p. 444–6), poliomyelitis.
- Upper airway obstruction (foreign body, tumour, epiglottitis) (➡ Acute upper airway obstruction, p. 224–5).
- Chest trauma.
- Anaphylaxis (➡ Anaphylaxis, p. 342).

Respiratory failure: investigations

Urgent investigations

- ABG: on air immediately, or if very unwell while on O_2 (note FiO_2).
- CXR (see Fig. 2.1).
- ECG: look for signs of PE (tachycardia, RBBB, anterior T-wave changes, RAD, rarely $S_1Q_3T_3$;  Pulmonary embolism (PE): assessment, p. 126), tachyarrhythmias, or myocardial ischaemia.
- Blood tests: FBC (anaemia, leucocytosis), U&Es, glucose.
- Inspect sputum: yellow, green, mucoid, streaky, or frank blood.
- FEV_1 and FVC: if suspected muscle weakness (e.g. GBS).
- Septic screen: sputum culture, blood cultures if febrile or if CXR suggests infection.

Where indicated, consider

- Aspirin and paracetamol levels.
- Plasma and urine for toxicology.
- Urinalysis for glucose and ketones.
- Examine the CXR systematically for any abnormality.

CXR assessment

- Consolidation/alveolar shadowing: may be lobar or patchy. Presence of an air bronchogram suggests pneumonia.
- Pulmonary oedema due to LVF (cardiogenic): typically perihilar ('bat-wing'), upper lobe venous congestion, Kerley B lines in peripheral lung fields, $\pm$ pleural effusions, $\pm$ cardiomegaly.
- Non-cardiogenic pulmonary oedema (ARDS/ALI): typically peripheral alveolar shadowing $\pm$ air bronchogram, *no* upper lobe venous congestion, Kerley B lines, pleural effusions, or cardiomegaly.
- Pleural effusions.
- Masses suggesting bronchogenic carcinoma.
- PE: wedge-shaped peripheral opacities, small pleural effusions, localized areas of oligaemia, enlarged PA.
- Pneumothorax (distinguish from large bullae).
- Trauma/rib fractures.
- Interstitial lung disease: small lung fields, interstitial reticulonodular shadowing peripherally and basally.

Respiratory failure: management

See ➡ Neuromuscular respiratory failure: assessment, pp. 440–1 for neuromuscular respiratory failure.

The severity of respiratory failure depends upon response to O_2 . Failure of hypoxia to correct on 40–60% O_2 or progressive hypercapnia implies that non-invasive or mechanical ventilation may be necessary, depending on the clinical condition and underlying cause.

Poor prognostic signs on presentation include

- Inability to speak due to dyspnoea.
- RR ($>40/\text{min}$).
- PEF $\leq 33\%$ of predicted in acute asthma.
- Tachycardia (HR $\geq 100\text{bpm}$) or bradycardia (HR $\leq 60\text{bpm}$).
- Exhaustion or coma (ventilatory support is required urgently).
- Stridor (this indicates upper airway obstruction; ➡ Acute upper airway obstruction, pp. 224–5).
- Pulse oximetry saturation of $<90\%$.
- Shock (tachycardia + hypotension). May indicate tension pneumothorax (➡ Tension pneumothorax, p. 216), severe LVF (➡ Pulmonary oedema: assessment, pp. 92–3), severe pneumonia (p ➡ Acute pneumonia: management, pp. 176–7), or large PE (➡ Pulmonary embolism (PE): assessment, p. 126).

Hypercapnia is the end-result of many causes of respiratory failure (including asthma and pneumonia), not just COPD, and indicates a tiring patient. Even if relatively elderly, the patient may respond well to ventilation, with a satisfactory final outcome, depending on the disease and premorbid condition.

General resuscitation (ABC)

- Ensure the airway is patent and the mouth is clear.
- If stridor is present, request anaesthetic and/or ear, nose, and throat (ENT) assistance urgently (➡ Acute upper airway obstruction, pp. 224–5).
- Sit the patient up (unless hypotensive), and administer O_2 at 60% unless there is a history of COPD (use 24–28% O_2).
- Ensure that respiratory effort is adequate and effective (measure RR and assess the depth of respiration); use pulse oximetry to monitor the P_aO_2 .
- If the patient is exhausted, with a failing respiratory drive, call for anaesthetic assistance and consider urgent transfer to ITU (see Box 2.13).
- In comatose patients with poor respiratory effort, consider drug overdose with opiates (pinpoint pupils) or benzodiazepines. Give naloxone 200–400 micrograms (2–4 micrograms/kg) IV bolus, followed by an infusion, depending on response, and/or IV flumazenil (200 micrograms over 15s, then 100 micrograms at 60s intervals if required—max. total dose 1mg (2mg if on ITU)).
- Methods of respiratory support are discussed under ➡ Principles of respiratory support, pp. 826–7.
- Secure IV access.

- Measure BP and HR; look for signs of cardiac failure (raised JVP, inspiratory crackles, oedema) or signs of PE (raised JVP, tachycardia, hypotension, normal breath sounds $\pm$ pleural rub).

See Box 2.14 for management key points.

Box 2.13 Indications for intensive care

- Progressive exhaustion or impaired conscious level.
- Shock not responding rapidly to initial resuscitation.
- Respiratory failure not responding rapidly to initial therapy.

Box 2.14 Management key points: respiratory failure

- Early ABG analysis is important to distinguish type 1 from type 2 respiratory failure and to determine the need for ventilatory assistance.
- History and examination taken together will usually suggest an aetiology.
- Treatment often revolves around correcting the underlying problem (e.g treating the LRTI), while supporting gas exchange (e.g with NIV).
- Remember there are non-respiratory causes for respiratory failure (neurological conditions, cardiac disease, and drug overdose).
- Involve ITU early if poor prognostic signs in a patient who may benefit from (and be appropriate for) mechanical ventilation.

Adult respiratory distress syndrome 1

ALI and its more severe subset ARDS result from the development of excessive pulmonary inflammation in response to initial injury, such as sepsis, which may be pulmonary or extra-pulmonary in origin. It is characterized by injury to the alveolar epithelial and endothelial barriers of the lung, acute inflammation, and protein-rich pulmonary oedema, leading to acute respiratory failure. Often occurs in the setting of multi-organ failure (MOF).

Diagnostic criteria

- Acute onset of respiratory failure with one or more risk factors (see Box 2.15).
- Hypoxaemia:
 - ALI: ratio P_aO_2 (kPa): $\dot{F}iO_2 < 40$.
 - ARDS: ratio P_aO_2 (kPa): $\dot{F}iO_2 < 27$.
- Bilateral infiltrates on CXR.
- PCWP < 19 mmHg, with normal colloid oncotic pressure [in patients with hypoalbuminaemia, the critical PCWP is approximately serum albumin (g/L) $\times 0.57$] or clinical exclusion of cardiac failure.

Investigations

- CXR.
- ABG (consider arterial line as regular samples may be required).
- Take blood for FBC, U&Es, LFTs and albumin, coagulation, cross-match, and CRP.
- Septic screen (culture blood, urine, and sputum).
- ECG.
- Consider drug screen, amylase if history suggestive.
- PA catheter to measure PCWP, cardiac output, and mixed venous O_2 saturation and to allow calculation of haemodynamic parameters.
- Other investigations if appropriate:
 - CT chest.
 - BAL for microbiology and cell count (? eosinophils).
 - Carboxyhaemoglobin estimation.

Management

See Box 2.16 for management key points.

- Almost all cases of ALI alone will require HDU/intensive care unit (ICU) care: liaise early.
- The main aim is to identify and treat the underlying cause, while providing support for organ failure:
 - Respiratory support to improve gas exchange and correct hypoxia.
 - Cardiovascular support to optimize O_2 delivery to tissues.
 - Reverse or treat the underlying cause.

Many drugs trialled have been aimed at inhibiting the inflammatory cascade and preventing injurious inflammation. More recently, cell-based therapy has focused on redirecting the immune/inflammatory response to a reparative state.

Box 2.15 Disorders associated with the development of ARDS

Direct lung injury

- Aspiration:
 - Gastric contents.
 - Near drowning.
- Inhalation injury:
 - Noxious gases.
 - Smoke.
- Pneumonia:
 - Any organism.
 - PCP.
- Pulmonary vasculitides.
- Pulmonary contusion.
- Drug toxicity or overdose:
 - O₂.
 - Opiate overdose.
 - Bleomycin.
 - Salicylates.

Indirect (non-pulmonary) injury

- Shock.
- Septicaemia.
- Amniotic or fat embolism.
- Acute pancreatitis.
- Massive haemorrhage.
- Multiple transfusions.
- DIC.
- Massive burns.
- Major trauma.
- Head injury:
 - Raised ICP.
 - Intracranial bleed.
- Cardiopulmonary bypass.
- Acute liver failure.

Box 2.16 Management key points: ARDS

- Caring for the patient with severe ALI/ARDS is a major challenge which resides predominantly with the ITU physician.
- Early diagnosis and intervention is key to prognosis/survival outcome.
- Lung-protective ventilation and optimization of V/Q matching, alongside treatment of the underlying disease process driving the injurious inflammation, is the crux of management.
- Some of the as yet unproven rescue therapies, including cell-based therapy, hold promise for the future management of this life-threatening condition.

Adult respiratory distress syndrome 2

Respiratory support

Spontaneously breathing patient

- In very mild ALI, hypoxia can be corrected with $\uparrow$ inspired O_2 concentrations (FiO_2 40–60%).
- Patients invariably require higher O_2 concentrations (non-rebreather masks with reservoir FiO_2 ~60–80%) or CPAP (➡ Continuous positive airways pressure, p. 827). Consider transfer to HDU/ICU.
- Indications for mechanical ventilation:
 - Inadequate oxygenation ($P_aO_2 < 8\text{kPa}$ on $FiO_2 > 0.6$).
 - Rising or elevated P_aCO_2 ($> 6\text{kPa}$).
 - Clinical signs of incipient respiratory/cardiovascular failure.

Mechanical ventilation

This is the realm of the ICU physician. The main aim is to improve oxygenation/ventilation, while minimizing the risk of further ventilator-induced lung injury, termed lung-protective ventilation. Lung-protective ventilation should be implemented immediately because of the excellent evidence that low tidal volume and low inspiratory pressure ventilation improve survival rates.

General principles

- Controlled mechanical ventilation with sedation [$\pm$ neuromuscular blockade (NMB)]. By preventing skeletal muscle activity, NMB increases chest compliance, improves patient–ventilator synchrony, and reduces airway pressures, reducing ventilator-associated lung injury (VALI).
- Ventilation with smaller tidal volumes is associated with improved outcome, compared to the traditional approach.
- PEEP improves oxygenation in most patients and allows reduction in FiO_2 . Usual starting level is 5–10 cmH_2O , with optimal levels in the range of 10–15 cmH_2O . Beware of hypotension due to reduction in venous return.
- The use of smaller tidal volumes may impair CO_2 clearance, with resulting acidosis despite high ventilatory rates (20–25 breaths/min). Gradual increases in pCO_2 (up to ~13 kPa) are well tolerated in most patients, and acidosis ($pH < 7.25$) can be treated with IV bicarbonate, the so-called permissive hypercapnia.

Adult respiratory distress syndrome 3

Cardiovascular support

- Arterial line is essential for continuous BP measurements. Other invasive monitoring is invariably used [PA catheter, pulse contour cardiac output (PiCCO), oesophageal Doppler], but their individual roles and effects on outcome are unclear.
- Most patients are haemodynamically compromised due to the underlying condition and/or ventilatory management, and benefit from fluid resuscitation. This may risk worsening capillary leak in the lung and compromise oxygenation/ventilation. Aim for a low-normal intravascular volume, while maintaining the cardiac index and MAP.
- Inotrope and/or vasopressor support is commonly required, and the choice of agent is usually decided on a combination of clinical evaluation and invasive haemodynamic monitoring. Agents commonly employed include dobutamine, dopamine, adrenaline, and NA.
- Repeated assessment is essential.

Ongoing management

- Look for, and treat, a precipitant (see Box 2.13).
- Sepsis:
 - Fever, neutrophilia, and raised inflammatory markers are common in ALI/ARDS and do not always imply sepsis.
 - A trial of empiric antibiotics, guided by possible pathogens and following an appropriate septic screen (consider BAL once intubated and stable), should be considered. Antibiotics should be modified or discontinued in light of microbiological results.
 - Indwelling CVP catheters are a common source of sepsis.
 - Consider low-dose steroid infusion.
- Renal failure: common and may require renal replacement therapy (RRT) to control fluid balance and blood biochemistry.
- Enteral feeding: helps maintain the integrity of the gut mucosa and is associated with a lower risk of systemic sepsis, when compared to parenteral feeding [total parenteral nutrition (TPN)]. Delayed gastric emptying and reduced gut motility are common in ICU patients and may respond to prokinetic drugs (metoclopramide, erythromycin) or may require nasojejunal feeding. Stress ulcer prophylaxis (H_2 -blockers) should be considered if mechanical ventilation >48h or MOF.
- Coagulopathy: common and, if mild, does not require therapy. If severe/DIC, expert advice should be sought.
- Steroid therapy:
 - Consider corticosteroids for patients with life-threatening hypoxaemia that has failed to respond to previous therapies. If no improvement in P_aO_2/FiO_2 , compliance, and P_aCO_2 within 72h, then discontinue treatment. If there is benefit, treatment can be extended, but optimal duration is currently unknown.

- *Emerging therapy:*
 - Statins, insulin, ACEI, and macrolides all have anti-inflammatory and immunomodulatory $\pm$ antithrombotic actions. Conflicting evidence exists with regard to the mortality benefit associated with any individual treatment or indeed combinations of drugs in ALI/ARDS. Macrolides show particular promise in pneumonia-induced ALI, as they have the added benefit of antimicrobial activity.
 - Cell-based therapy, particularly use of mesenchymal stem/stromal cells, is an attractive option being extensively investigated.
- *Sepsis:* evidence suggests that some patients with refractory septic shock (ongoing/increasing vasopressor requirements) may have 'relative' or 'functional' adrenal insufficiency and may benefit from 'supraphysiological' steroid replacement (200–300mg/day of hydrocortisone). Identification of patients likely to benefit is unclear at present, but adrenocorticotrophic hormone (ACTH) stimulation test may help discriminate.

See Box 2.17 for causes of sudden deterioration in ARDS.

Box 2.17 Causes of sudden deterioration in ARDS

Respiratory

- Pneumothorax.
- Bronchial plugging.
- Displaced ETT.
- Pleural effusion (haemothorax).
- Aspiration (e.g. NG feed).

Cardiovascular

- Arrhythmia.
- Cardiac tamponade.
- MI.
- GI bleed ('stress' ulcer).
- Septicaemia.

Outcome

- Outcome for ALI/ARDS has improved in recent years, with overall mortality rates of ~40%.
- Patients with ALI/ARDS and sepsis, liver disease, non-pulmonary organ dysfunction, or advanced age have higher mortality rates.
- In survivors, although formal lung function tests are abnormal, respiratory compromise at 1–2 years is unusual.
- There is increasing evidence that survivors suffer considerable neuromuscular and psychological disability. This may reflect the period of prolonged critical illness, rather than be specific for ALI/ARDS.

Further reading

- Diaz JV, Brower R, Calfee CS, Matthay MA. Therapeutic strategies for severe acute lung injury. *Crit Care Med.* 2010;**38**:1644–50.
- Sweeney RM, Griffiths M, McAuley D. Treatment of acute lung injury: current and emerging pharmacological therapies. *Semin Respir Crit Care Med.* 2013;**34**:487–98.

Pneumothorax: assessment

Presentation

Most individuals presenting to hospital with a spontaneous pneumothorax have no recognized underlying lung disease. The most common presenting symptoms are:

- **Breathlessness:** usually abrupt in onset (young, fit patients may have very little, but patients with COPD or asthma may present with sudden deterioration). The presence of breathlessness influences the management strategy.
- **Chest pain:** dull, central, heavy; or there may be a pleuritic element.
- **In an inpatient, consider the diagnosis in anyone who is:**
 - Breathless after an invasive thoracic procedure (e.g. subclavian vein cannulation).
 - Increasingly hypoxic or has rising inflation pressures on mechanical ventilation.

Causes

- **Primary/spontaneous:** healthy subjects, no known underlying lung disease. More common in tall, young men who smoke, aged 20–40 years. Probably due to rupture of apical subpleural blebs/bullae.
- **Secondary/spontaneous (SSP):** pleural rupture due to underlying lung disease: emphysema, fibrosing alveolitis, cystic fibrosis, sarcoidosis. Symptoms tend to be greater in SSP, even if the pneumothorax is relatively small in size.
- **Infection:** cavitating pneumonia, e.g. staphylococcal, lung abscess, TB, PCP.
- **Trauma:** particularly chest trauma in road traffic accident (RTA).
- **Iatrogenic:** after pleural biopsy or aspiration, transbronchial biopsy, percutaneous lung biopsy, subclavian vein cannulation, and mechanical ventilation with high airway pressures.

Investigations: the chest radiograph

- The classical clinical signs may not always be present.
- Standard erect CXR in inspiration is recommended for initial diagnosis.
- In a supine patient, a pneumothorax may not be easy to see. Look for hyperlucency of one lung field or a line parallel to the chest wall (caused by retraction of the right middle lobe). An erect CXR may show blunting of the costophrenic angle on the affected side.
- If a patient has COPD and marked bullous disease, take care that the suspected pneumothorax is not a large, thin-walled bulla. CT scanning is recommended for uncertain or complex cases.

Signs of a significant pneumothorax

- Tension pneumothorax: midline shift away from the pneumothorax, raised or obstructed JVP, hypotension, tachycardia, shock.
- Size of pneumothorax: percentages of a pneumothorax are hard to estimate and less important than the degree of clinical compromise; classify according to the size of the visible rim between the lung margin and the chest wall at the level of the hilum on the CXR:
 - Small pneumothorax: visible rim $<2\text{cm}$.
 - Large pneumothorax: visible rim $>2\text{cm}$.

(NB A large pneumothorax approximates to a 50% loss of lung volume.)

- Hypoxia: $P_a\text{O}_2 \leq 10\text{kPa}$ on air (may simply reflect underlying lung disease).
- Severe dyspnoea.

Pneumothorax: management

See Figs. 2.2 and 2.3. See Box 2.18 for management key points.

Who to discharge from A&E

Patients with primary spontaneous pneumothorax (PSP) or SSP and breathlessness associated with any size of pneumothorax should undergo active intervention, as well as supportive treatment (including O_2).

- Small PSP, rim of air <2cm on CXR, no significant dyspnoea, and no underlying chronic lung disease.
- Large PSP following successful aspiration (<2cm rim of air on repeat CXR), no significant dyspnoea or underlying lung disease.
- All patients with an SSP should be referred early to a chest physician.
- Follow-up in chest clinic in 10–14 days with a repeat CXR.
- Advise the patient to return to A&E if breathless or increasing chest pain.
- Air travel should be avoided until full resolution.

Who to admit for observation

- All patients with pneumothorax secondary to trauma or with an underlying lung disease, even if aspiration has been successful—discharge after 24h if follow-up CXR shows no recurrence.
- Patients in whom aspiration has failed to re-expand the lung fully.
- Give O_2 (>35% unless there is clinical evidence of COPD, in which case start with 24–28% and check ABGs). This accelerates the reabsorption of the pneumothorax up to 4-fold. Most of the pneumothorax is nitrogen (N_2) (air), and supplemental O_2 decreases the partial pressure of N_2 in blood, increasing the gradient for its reabsorption.

Attempt chest aspiration in patients with

- Primary pneumothorax: all large primary pneumothoraces, whether symptomatic or not.
- Secondary pneumothorax: all small secondary pneumothoraces, only if asymptomatic and <50 years. Admit for observation, and if there is minimal or no pneumothorax on CXR after 24h, discharge with follow-up in chest clinic in 10–14 days with CXR.
- Needle aspiration should not be repeated, unless there were technical difficulties.

Proceed to intercostal chest tube drainage in patients with

- Primary pneumothorax: failed aspiration.
- Secondary pneumothorax: small pneumothorax if symptomatic or >50 years; failed aspiration after one attempt.
- Miscellaneous: associated hydro- or haemopneumothorax, all mechanically ventilated patients with a pneumothorax, all patients with a pneumothorax requiring interhospital transfer.

- The technique for insertion of an intercostal drain is described under ➡ Insertion of a chest drain 1, pp. 838–9 and ➡ Insertion of a chest drain 2, p. 840.
 - If the lung has re-expanded and the drain is not bubbling, wait 24h and repeat CXR to exclude recurrence, and remove the drain.
 - A collapsed lung and bubbling drain suggests persistent air leak, and suction may be required.
 - A collapsed lung and no bubbling suggests the drain is blocked, displaced, or clamped. If a new drain is required, it should be through a new incision.
 - Patients with a persistent air leak should be discussed with a cardiothoracic surgeon at 48h.
- Use of suction:
 - Suction should not be routine. Caution is required because of the risk of re-expansion pulmonary oedema.
 - High-volume, low-pressure suction systems are recommended.

Practice points

- There are **NO** indications in the standard management for a pneumothorax for clamping chest drains. If patients are to be moved, keep the drain bottle below chest height, but **DO NOT CLAMP**.
- **NEVER** clamp a chest drain, unless you know what you are doing.

Box 2.18 Management key points: pneumothorax

- Assess for breathlessness, alongside making the clinical/radiological diagnosis, as this influences the management strategy.
- Determine whether primary or secondary, and the size and degree of clinical compromise. Support with O_2 .
- Tension pneumothorax is life-threatening and should be diagnosed clinically (not on CXR) and treated with emergency decompression followed by drainage.
- Attempted aspiration is appropriate for PSP and small asymptomatic SSP (1–2cm).
- Admit all SSPs for observation, and inform the chest team.
- Involve thoracic surgeons within 3–5 days if persistent air leak post-intercostal drainage.

Acute pneumothorax: management

See Figs. 2.2 and 2.3.

Primary pneumothorax

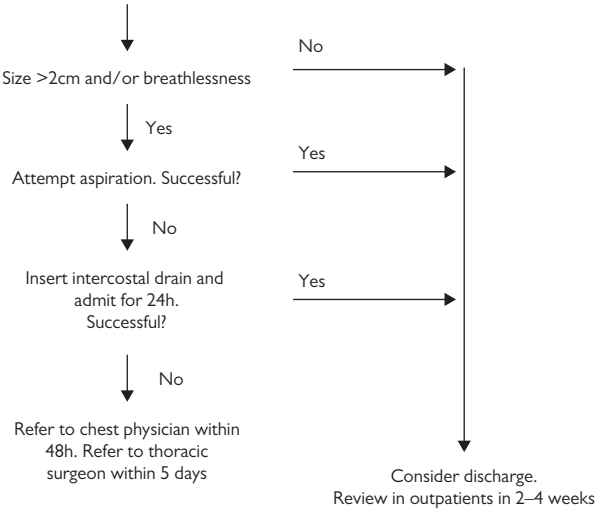
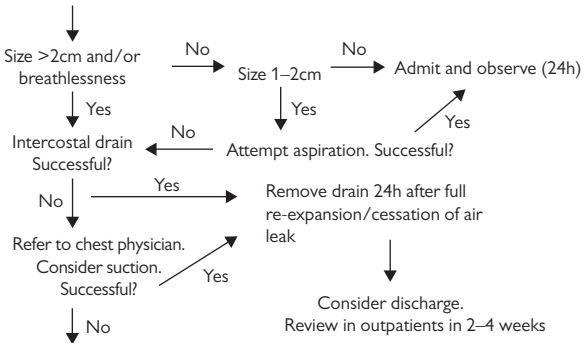


Fig. 2.2 Primary pneumothorax: management.

Source: data from *Management of spontaneous pneumothorax*, British Thoracic Society Pleural Disease Guideline 2010, BMJ Publishing Group Ltd. <https://www.brit-thoracic.org.uk/document-library/clinical-information/pleural-disease/pleural-disease-guidelines-2010/pleural-disease-guideline>

Secondary pneumothorax (age >50 + significant smoking history/underlying lung disease)

Early discussion with thoracic surgeon after 3 days

Fig. 2.3 Secondary pneumothorax: management.

Source: data from *Management of spontaneous pneumothorax*, British Thoracic Society Pleural Disease Guideline 2010, BMJ Publishing Group Ltd. <https://www.brit-thoracic.org.uk/document-library/clinical-information/pleural-disease/pleural-disease-guidelines-2010/pleural-disease-guideline>

Tension pneumothorax

- Usually seen in patients receiving mechanical ventilation or post-CPR.
- Patient is usually distressed and tachypnoeic, with cyanosis, profuse sweating, and marked tachycardia and hypotension.
- This requires immediate attention.

Management

- Do not leave the patient unattended. Give maximal inspired O_2 to reverse hypoxia.
- Insert an 18G (green) cannula (or the largest available), perpendicular to the chest wall, into the second intercostal space in the mid-clavicular line on the side of the pneumothorax on clinical examination (reduced breath sounds and trachea deviated away). Relief should be almost immediate. Leave the cannula in place until the air ceases to rush out.
- Insert a chest drain as soon as possible.
- If no air rushes out when the cannula is inserted, the patient does not have a tension pneumothorax and the cannula should be removed.

Haemoptysis: assessment

Presentation

- Haemoptysis is coughing up of blood from the lungs or tracheobronchial tree (see Box 2.19).
- Massive haemoptysis is defined as $\geq 400\text{mL}$ over 3h or $\geq 600\text{mL}$ over 24h. The common causes of *massive* haemoptysis are bronchiectasis, bronchial carcinoma, infection (e.g. TB, lung abscess, or aspergilloma), or trauma.
- Often the cause is obvious from the history. Patients with large bleeds may be able to locate the site of bleeding by a 'gurgling' within the chest. Ask specifically for smoking and drug history.
- Examine for an underlying cause (see Box 2.19) and to assess the haemodynamic and respiratory effects of the bleed.
- Consider that the blood may be coming from somewhere other than the lungs: upper respiratory tract, GI tract, nasopharynx.

Poor prognostic factors

These include:

- Increasing age.
- Pre-existing lung or cardiac disease.
- Respiratory compromise (rate, cyanosis).
- Hypoxia ($P_a\text{O}_2 \leq 10\text{kPa}$ on air).
- Ongoing haemoptysis of large amounts of fresh blood.
- Shock (postural or supine hypotension—rare).

Box 2.19 Common causes of haemoptysis

Lung disease

- Bronchiectasis and cystic fibrosis ($\pm$ infection).
- Bronchogenic carcinoma.
- Infection:
 - TB.
 - Pneumonia.
 - Lung abscess.
 - Aspergilloma.
- Bronchitis.
- Trauma.
- AV malformation.

Cardiovascular

- PE.
- LVF.
- Mitral stenosis.
- Congenital heart disease with pulmonary hypertension.
- Aortic aneurysm.

Systemic vasculitis

- SLE.
- Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis (WG).
- Goodpasture's syndrome.
- Microscopic polyangiitis.

Haemoptysis: management

Initial management

See Box 2.20 for management key points.

Stabilize the patient

- Massive haemoptysis should usually be managed at a hospital with cardiothoracic surgical backup, and urgent transfer should be considered if this is not available.
- Give high inspired O_2 .
- Place the patient in the recovery position, with the bleeding lung down (if it is known which side the bleeding is from) to try to keep the unaffected lung free of blood.
- If aspiration of blood is threatened, get anaesthetic help urgently; anaesthetize, intubate, and ventilate. A double-lumen ETT may be used to isolate the lungs, but the narrow lumen may make subsequent flexible bronchoscopy difficult.
- Insert a large-bore peripheral cannula, followed by a central line if indicated; the internal jugular route is preferred to minimize the risk of pneumothorax.
- Support the circulation; haemoptyses are rarely severe enough to warrant transfusion. But cross-match 2–4U if bleeding ongoing. Monitor the urine output, pulse, BP, and, if appropriate, CVP.

Investigations

All patients should have the following:

- Blood for FBC, U&Es, coagulation studies, and cross-match.
- ABGs.
- ECG.
- CXR.
- Sputum (microscopy and culture, cytology).
- Flexible bronchoscopy.

Diagnose the source of bleeding

- **CXR:** this should be examined systematically for a mass lesion $\pm$ hilar nodes, bronchiectasis (tramline shadows), and old or new cavities which may suggest aspergillomas. Look for causes of minor haemoptysis, if this is the current problem.
- **Fibreoptic or rigid bronchoscopy:** this should be performed urgently in all cases of massive haemoptysis. This is unlikely to localize the exact source but may help localize the lung or lobe affected, to guide surgeons or radiologists. Bleeding may be arrested by endoscopically administered adrenaline (1mL of 1:10 000) or, in massive haemoptysis, a balloon catheter may be inflated for 24–48h within a segmental or sub-segmental bronchus.
- **Selective pulmonary angiography:** can identify the bleeding source in 90% of patients and, when combined with embolization, is effective in controlling bleeding in up to 90%. Multiple procedures may be necessary.
- **High-resolution CT chest:** may help identify parenchymal lesions and peripheral endobronchial lesions.

Specific therapeutic interventions

- Correct coagulopathy: if the haemoptysis is relatively minor, it may be sufficient to correct an excessively elevated INR to a therapeutic range (INR 1.5–2.0) with FFP. In patients with a prosthetic valve and massive haemoptysis, the clotting must be normalized as best as possible. Discuss with your local haematologists or cardiologists. Support platelets if $<50 \times 10^9/L$.
- Patients with minor haemoptysis should be fully investigated (see Box 2.21). No cause is found in ~10%.
- Patients with massive haemoptysis should undergo urgent fibreoptic bronchoscopy to locate the bleeding source.
- Angiography and embolization should be considered for all patients with massive haemoptysis prior to surgery.
- If angiography is not available, patients who continue to bleed $>600\text{mL/day}$ or who have an identifiable lesion (e.g. lung abscess, aspergilloma, trauma) should have definitive surgery.
- Discuss all cases of haemoptysis with the chest team. Patients with massive haemoptysis should be managed in a specialist centre with appropriate cardiothoracic and radiological backup. Transfer the patient (ventilated if unstable) if the patient is fit enough.
- Infection is a common precipitant (e.g. in bronchiectasis). Consider antibiotics (e.g. co-amoxiclav 1g IV q6–8h or cefotaxime 2g IV q8h) after appropriate cultures. TB or lung parasites will require specific antimicrobial therapy.

Box 2.20 Management key points: haemoptysis

- Determine if massive ($>400\text{mL}$ over 3h or $>600\text{mL}$ over 24h) or minor, and, if possible, where the blood is coming from to inform the management strategy.
- Stabilize the patient, and determine the best place of care (may involve transfer to a hospital with cardiothoracic surgical backup).
- Correct coagulopathy, and consider empirical antibiotics as infection is a common precipitant.
- Discuss all cases of haemoptysis with the chest team. Patients with minor haemoptysis should be fully investigated (often as outpatients).

Box 2.21 Further investigation of haemoptysis

- Autoantibodies [ANA, anti-neutrophil cytoplasmic antibody (ANCA), anti-glomerular basement membrane (GBM) antibody].
- Serum for *Legionella* serology.
- *Aspergillus* precipitins.
- CT chest.
- V/Q scan.
- Echo.
- Pulmonary and bronchial artery angiogram.
- Lung biopsy.
- PFTs with transfer factor.

Pleural effusions

Presentation

- Dyspnoea.
- Chest discomfort or sensation of heaviness.
- Symptoms of malignancy: loss of appetite, weight, and energy.
- Symptoms of infection: fever, cough, sputum, night sweats.

Severity depends on

- Speed of onset (e.g. traumatic or post-procedural).
- Haemodynamic compromise (hypotension, tachycardia).
- Hypoxia or respiratory failure.
- Presence of underlying disease (e.g. heart failure, COPD).

Causes

Transudate (protein <30g/L)

- Raised venous pressure:
 - Cardiac failure.
 - Constrictive pericarditis.
 - Fluid overload.
- Hypoproteinaemia:
 - Nephrotic syndrome.
 - Cirrhosis with ascites.
 - Protein-losing enteropathy.
- Miscellaneous:
 - Hypothyroidism.
 - Meigs' syndrome.
 - Yellow nail syndrome.

Exudate (protein >30g/L)

- Infection:
 - Pneumonia.
 - Empyema (bacterial or TB).
 - Subphrenic abscess.
- Malignancy:
 - Primary bronchial.
 - Mesothelioma.
 - Secondary (and lymphoma).
 - Lymphangitis carcinomatosa.
- Miscellaneous:
 - Haemothorax (trauma, iatrogenic).
 - Chylothorax (thoracic duct trauma).
 - Autoimmune (RA, SLE, Dressler's).
- Pancreatitis.

Management

See Box 2.22 for management key points.

- If acute, then stabilize the patient and insert a chest drain.
- If effusion is chronic, then reach a diagnosis and treat accordingly.
- Image guidance: a recent CXR should be available prior to performing aspiration/drainage. Thoracic US guidance is strongly recommended for all procedures for pleural fluid. Prior marking of the spot for subsequent remote intervention is not recommended, except for large pleural effusions.

Acute massive effusion

- Give O₂.
- IV access: via a wide-bore cannula or an internal jugular central line (being careful not to cause further lung injury).
- Take blood: for FBC, clotting, and urgent cross-match (6U).
- Correct coagulopathies.

- Restore circulating volume: if BP low or tachycardic, then give a plasma expander 500mL stat, according to the size of effusion drained and response.
- Insert a chest drain (➡ Insertion of a chest drain 1, pp. 838–9 and ➡ Insertion of a chest drain 2, p. 840). The drain should be left unclamped and allowed to drain freely, and the amount drained should be recorded.

Indications for specialist referral

- Traumatic haemothorax should be referred to cardiothoracic surgeons.
- Haemothorax secondary to procedures should be referred if the patient is shocked and/or there is ongoing significant blood loss requiring transfusion at a rate $\geq 1\text{U}$ every 4h (approximately).
- When in doubt, discuss the case with the surgical team.

Practice points

If there is ↓movement of one side of the chest, that is the side of pathology (e.g. fluid, infection, pneumothorax).

Box 2.22 Management key points: pleural effusion

- Assess size, chronicity, and degree of patient compromise.
- Correct hypoxia and assess gas exchange.
- Investigate the underlying cause if unknown.
- Aspirate a pleural fluid sample under US guidance.
- Determine if transudate or exudate, and look for evidence of pleural infection (check pH, and send sample for biochemistry, microscopy/microbiology, and cytology).
- If drainage required, beware of re-expansion pulmonary oedema and limit to 1.5L/day.
- Involve the chest team in all cases of malignant effusion, pleural effusions where the diagnosis is unclear, slow-to-resolve cases (e.g. trapped lung), or cases where pleurodesis may be considered.

Chronic massive effusion

A unilateral chronic effusion will usually have accumulated over weeks or perhaps even months. The most common cause is malignancy. Empyema, TB, autoimmune diseases (e.g. rheumatoid), and cirrhotic ascites with transdiaphragmatic movement are alternative aetiologies.

Investigations

- Diagnostic aspiration under US guidance. A sample should then be withdrawn (50mL) and split into three for:
 - *Biochemistry*:
 - Protein $\geq 30\text{g/L}$ implies an exudate.
 - Protein $< 30\text{g/L}$ implies a transudate.
 - LDH to assess Light's criteria (see Box 2.23).
 - pH < 7.2 suggests a possible empyema.
 - Glucose $< 3.3\text{mmol}$ suggests a possible empyema (also seen in TB and autoimmune-related effusions).
 - Amylase if acute pancreatitis suspected.
 - Triglycerides if chylothorax suspected.
 - *Microscopy/microbiology*:
 - Turbid fluid with neutrophils implies an infection.
 - Bloodstained fluid implies malignancy but may be a haemothorax (check fluid haematocrit: if $> 1/2$ blood haematocrit, suspect haemothorax).
 - ZN staining for acid-fast bacilli (AFB) (+ve in only 20% of pleural TB).
 - Culture for TB and routine culture.
 - *Cytology*: for primary and secondary tumours. Positive in 60%, so negative does not exclude malignancy.
- Pleural biopsy should be performed if malignancy or TB is suspected.
- Chest CT with contrast may help differentiate benign from malignant disease, pleural thickening, mesothelioma, or intrapulmonary pathology.

Management

- The main priorities are diagnosis (if unknown) and symptomatic relief.
- Advice should be sought from the respiratory team for symptomatic/malignant effusions.
- The fluid may be drained by aspiration or by insertion of a small-bore intercostal drain (10–14F) (➡ Insertion of a chest drain 1, pp. 838–9 and ➡ Insertion of a chest drain 2, p. 840), which should be clamped and released to drain 1.5L/day (this is the only instance when a chest drain may be clamped).
- Drainage of $> 1.5\text{L}$ on a single occasion may result in reperfusion pulmonary oedema so is not recommended.
- If the malignant effusion reaccumulates rapidly, consider chemical or surgical pleurodesis, unless lung significantly trapped. Seek advice from the respiratory team.
- In cases of 'trapped lung', indwelling catheters offer a better approach to management than recurrent aspiration/drainage.

Empyema

This is a serious complication of bacterial chest infection (➡ Acute pneumonia: complications, p. 179). All effusions associated with sepsis or pneumonia should be tapped and pH assessed if non-purulent and pleural infection suspected.

- To avoid long-term scarring and loculated infection, the empyema requires urgent drainage by US guidance and usually the positioning of an intercostal drain.
- Frequently, drainage fails as the empyema organizes with dense adhesions producing loculations. This can be assessed by US. Surgical drainage may be required.
- Empyema should always be discussed with a respiratory physician or cardiothoracic surgeon.
- There is no indication for routine use of intrapleural fibrinolytics.
- All patients with pleural infection are high risk for the development of VTE and should receive adequate thromboprophylaxis unless contraindicated.

See Box 2.23 for Light's criteria for pleural fluid analysis.

Practice points

The sun should never set on an empyema! Patients with purulent/turbid pleural fluid (or positive Gram stain) should receive prompt pleural space chest tube drainage under image guidance (small-bore 10–14F will be adequate in most cases, with regular flushing to avoid blockage).

Box 2.23 Light's criteria for pleural fluid analysis

The pleural fluid is an exudate if one or more of the following criteria are met:

- Pleural fluid protein divided by serum protein >0.5 .
- Pleural fluid LDH divided by serum LDH >0.6 .
- Pleural fluid LDH more than two-thirds the upper limit of normal serum LDH level.

Further reading

British Thoracic Society, Pleural Disease Guideline Group (2010). *BTS pleural disease guideline 2010*.
🌐 <https://www.brit-thoracic.org.uk/document-library/clinical-information/pleural-disease/pleural-disease-guidelines-2010/pleural-disease-guideline>

Acute upper airway obstruction

Presentation

- Stridor: inspiratory noise. Generated by the collapse of the extrathoracic airway during inspiration.
- Breathlessness.
- Dysphagia.
- Inability to swallow secretions (hunched forward, drooling).
- Cyanosis.
- Collapse.

Ask colleagues to call a senior anaesthetist and for ENT assistance immediately, while you continue your assessment.

Identify the cause

(See Box 2.24.)

- *History*: sudden onset, something in the mouth or child playing with unsafe toy (foreign body), fever (epiglottitis, diphtheria, tonsillitis), hoarse voice (epiglottitis), sore throat (infective as listed), travel (Eastern Europe—diphtheria), smoker + longer history + systemic symptoms (? carcinoma), trauma.
- *Examination*: where an infective cause is suspected, then examination of the oropharynx must be undertaken in an area where the patient may be immediately intubated, with an anaesthetist standing by.
- Fever, drooling, stridor. Bull neck, lymphadenopathy, pseudomembrane over the oropharynx (diphtheria). Swollen throat + epiglottis on direct/indirect laryngoscopy (epiglottitis).
- *Investigations*: do not delay treatment if the patient is in distress. If the patient is relatively stable, perform a CXR (foreign body) or lateral neck X-ray (swollen epiglottis). FBC, U&Es, ABGs.

Box 2.24 Causes of acute stridor

- Infective: acute epiglottitis, diphtheria, tonsillitis, or adenoiditis (children).
- Inhalation of foreign body.
- Tumour of the trachea or larynx.
- Trauma.
- Post-operative (thyroid surgery).

Indications for ITU/surgical referral

- Prior to examination of the oropharynx if infective cause suspected.
- Failure to maintain adequate airway or oxygenation.
- Inability to swallow secretions.
- Ventilatory failure ($P_aO_2 \leq 10\text{kPa}$, $P_aCO_2 \geq 6\text{kPa}$).
- Collapse.
- Severe dyspnoea.

Management

- If severe, liaise immediately with ITU and ENT or general surgeons (potential for urgent tracheostomy).
- Priorities are:
 - Stabilize the patient: ensure adequate airway.
 - Identify the cause of obstruction.
 - Specific treatment measures.

Stabilize the patient

- Take ABGs, and give high percentage O₂ (≥60%).
- If a clear cause of obstruction (foreign body, post-operative thyroid surgery) (see Box 2.24), then take appropriate measures to gain patient airway.
- If the patient is becoming increasingly exhausted or there is acute failure of ventilation, then summon colleagues and be prepared to intubate or perform a tracheostomy.

Foreign body

With total upper airway obstruction, perform the Heimlich manoeuvre (stand behind the patient, grip the wrists across the patient's upper abdomen, and tug sharply to raise the intrathoracic pressure and expel the foreign body). Otherwise perform a CXR, and liaise with the respiratory/ENT/cardiothoracic teams for retrieval under direct vision.

Epiglottitis

Usually *H. influenzae* type b, also *S. pneumoniae*. Treat with third-generation cephalosporin, e.g. cefotaxime 2g tds (adults). Children more likely to require intubation, but if any concerns over airway, then the patient (adult or child) should be monitored on ITU after anaesthetic assessment.

Diphtheria

Uncommon in the UK; occasionally seen in patients returning from abroad. Toxin-mediated problems include myocarditis and neuritis. Treat with diphtheria antitoxin + antibiotic eradication of organism (consult microbiology).

Tumour obstruction

Unlikely to cause life-threatening obstruction without warning symptoms over at least a few days. If significant stridor is present, then administer 200mg of hydrocortisone, and thereafter prednisolone 40mg od PO. If laryngeal origin, liaise with ENT regarding tracheostomy. Lung cancer in the trachea, or extrinsic cancer eroding into the trachea, will require urgent radiotherapy (or occasionally laser or cryotherapy via a bronchoscope).

Gastroenterological emergencies

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Acute upper gastrointestinal bleeding 1

Determine the source

- *History*: ask specifically about dyspepsia, alcohol, drug history [e.g. NSAIDs, anticoagulants, selective serotonin reuptake inhibitors (SSRIs), steroids], risk factors for liver disease, normal vomit prior to haematemesis (Mallory–Weiss tear, variceal bleed), previous GI bleeds, ulcers, or surgery.
- *Physical examination*: look for stigmata of chronic liver disease (including hepatomegaly and splenomegaly), scars of previous surgery, telangiectasia (Osler–Weber–Rendu syndrome), abdominal bruit, and bruises. Rectal examination may reveal melaena or semi-fresh blood.
- *Upper GI endoscopy*: should be done within 24h¹ of the bleed. It may be difficult to precisely locate the site of bleeding due to clots in the stomach, but it is easy to exclude possible areas of bleeding which may help decide further management. Remember upper GI bleeding in patients with cirrhosis has a non-variceal origin in ~30% of cases.
- *Selective arteriography*: of the coeliac axis and superior mesenteric or inferior mesenteric artery is of value when the bleeding site cannot be identified, usually after two or more negative endoscopies, and bleeding is brisk (0.5–1mL/min).
- *Barium studies or MRI*: may be used to diagnose small bowel causes of melaena [e.g. Crohn's disease (CD) or tumour]. Labelled RBC scans may also be useful. Meckel's scan may be useful in younger patients.
- *Capsule endoscopy*: is used to diagnose causes of occult or recurrent, but unidentified, GI bleeding.

General measures to stop the bleeding

- *Correct any coagulopathy*:
 - Platelet count below 50 000/mm³ should be treated with platelet support (6–12U of platelets).
 - If the patient is on anticoagulants, assess the need for anticoagulation before reversal. The annual risk of embolization in non-anticoagulated patients with prosthetic heart valves is 4% for aortic valves and 8% for mitral valves overall, with a greater risk with caged-ball valves. The annual risk of stroke in non-anticoagulated patients with AF is 3–5% (relative risk 2.5–3) but is much lower in those <75 years without comorbidity. Therefore, in patients with prosthetic valves, correct with prothrombin complex concentrate (PCC) or FFP (2–4U) and/or a very low dose of vitamin K (0.5–1mg IV). Otherwise, give PCC or FFP and IV vitamin K (10mg).
 - Cryoprecipitate may be required if fibrinogen levels are low.
 - Consider clotting product $\pm$ platelets if $\geq 4U$ of RBCs given.
 - The new oral anticoagulants (NOACs), such as rivaroxaban and dabigatran, have a lower risk of major bleeding than warfarin. However, currently, there are no reversal agents available (at the time of publication, several compounds are in clinical trials). NOACs generally have a short half-life. Hence, stop the drug, and transfuse with blood products, if necessary. The same principle applies for antiplatelets and heparin.

- *Serum calcium*: may fall after several units of citrate-containing blood transfusion. Give 10mL (4.5mEq) of calcium chloride for every 3–4U transfused. Supplement Mg^{2+} and phosphate (PO_4^{3-}), as necessary.
- *Ulcer-healing agents*: IV PPI, such as pantoprazole or omeprazole (80mg IV, followed by 8mg/h for 72h), post-endoscopic intervention.
- *Tranexamic acid* (0.5–1g IV tds or 1–1.5g PO tds): increases the levels of fibrinogen and may be helpful. Likewise, desmopressin may be useful in patients with renal failure.
- *Recombinant factor VIIa*: only consider its use when all other methods have failed (initial dose of 90 micrograms/kg).

References

1. National Institute for Health and Care Excellence (2012). *Acute upper gastrointestinal bleeding in over 16s: management*. Clinical guideline [CG141]. <https://www.nice.org.uk/Guidance/cg141>

Acute upper GI bleeding 2

Presentation

- Haematemesis (bright red, dark clots, coffee-ground).
- Melaena (black, sticky, smelly). This may arise from anywhere proximal to, and including, the caecum. Blood is cathartic and takes 4–6h to be passed. With massive bleeding (e.g. variceal), there may be dark clots in the stool. Other causes of dark stool include iron therapy, bismuth-containing drugs, liquorice, or drinks (red wine).
- Weakness/sweating and palpitations.
- Postural dizziness and fainting.
- Collapse or shock.

Causes

(See Table 3.1.)

Table 3.1 Causes of acute GI bleeding

Causes	Approximate percentage
Peptic ulcer	35–50
Gastroduodenal erosions	8–15
Oesophagitis	5–15
Varices	5–10
Mallory–Weiss tear	15
Upper GI malignancy	1
Vascular malformations	5
Rare miscellaneous	5 (e.g. Meckel's, CD)

Assessment of severity

It is essential to categorize patients at the time of admission into high or low risk of death [recent NICE guidelines advise using Blatchford scores (see Table 3.2) on admission].² Patients with a Blatchford score of >0 should be considered for endoscopy; if score = 0, can consider early discharge.

Most deaths occur in the elderly with comorbid disease.

In general, high-risk factors include the following:

- Age >60 years (30% risk of death if >90 years).
- Shock (SBP <100mmHg in patients <60 years or <120mmHg in patients >60 years). *Measure postural change* in BP in patients who are not shocked, and change in HR.
- Inappropriate bradycardia or HR >120bpm.
- Chronic liver disease.
- Other chronic disease (e.g. cardiac, respiratory, renal).
- Bleeding diathesis.
- ↓conscious level.

Management

Liaise with specialists early (on-call endoscopy team and surgeons). An experienced anaesthetist should be informed. Most patients will have stopped bleeding by the time they are seen; however, all upper GI bleeds should be taken seriously, as they may re-bleed in hospital, and mortality following a re-bleed is high.

Priorities are:

- To stabilize the patient: protect the airway and restore the circulating volume.
- To identify the source of the bleed.
- Definitive treatment of the cause of bleeding.

Table 3.2 Blatchford score*

The Blatchford score admission risk marker	Score value
Blood urea (mmol/L)	
≥6.5 to <8.0	2
≥8.0 to <10.0	3
≥10.0 to <25	4
≥25	6
Hb (g/L) for men	
≥120 to <130	1
≥100 to <120	3
<100	6
Hb (g/L) for women	
≥100 to <120	1
<100	6
SBP (mmHg)	
100–109	1
90–99	2
<90	3
Other markers	
Pulse ≥100bpm	1
Presentation with melaena	1
Presentation with syncope	2
Hepatic disease	2
Cardiac failure	2

* Reprinted from *The Lancet*, 356, Blatchford O *et al.*, 'A risk score to predict need for treatment for uppergastrointestinal haemorrhage', 1318–21, Copyright 2000, with permission from Elsevier.

References

2. National Institute for Health and Care Excellence (2012). *Acute upper gastrointestinal bleeding in over 16s: management*. Clinical guideline [CG141]. [J&R https://www.nice.org.uk/Guidance/cg141](https://www.nice.org.uk/Guidance/cg141)

Acute upper GI bleeding 3

Initial management

(See Box 3.1.)

- *Protect the airway*: position the patient on the side.
- *IV access*: insert 1–2 large-bore (14G–16G) cannulae into a peripheral vein for initial fluid resuscitation. If peripheral access is difficult, access via the jugular, subclavian, or femoral vein may be necessary. CVP monitoring (➡ Central line insertion, p. 790) allows early identification of bleeding and is useful to prevent overfilling. It is essential in older patients or in those with massive haemorrhage. A fall of 5cmH₂O over 2h suggests a re-bleed.
- Take blood for *Hb* and *packed cell volume (PCV)*: these do not fall until the plasma volume has been restored but, if low at presentation, suggests massive blood loss or acute-on-chronic bleeding. WCC may be elevated but usually <15 000/mm³. If WCC is elevated, look for sepsis (sepsis predisposes to haemorrhage). *Platelet count*: if low, suggests hypersplenism and chronic liver disease. *U&Es*: ↑urea out of proportion to creatinine (may be >100:1) indicates significant GI bleed. Check *PT* and *LFTs*, since liver disease is a common cause of GI bleeding; *group and save (G&S)* and *cross-match* 4–8U. Monitor venous blood gas (or ABG) in severely ill patients.
- *Restore the circulating volume*:
 - ↑HR, ↓BP, or a postural ↓BP or a postural ↑HR (by >30bpm) suggest a low intravascular volume. Give 500mL to 1L of crystalloids over 1h or normal saline, and continue until blood is available. Stable BP takes precedence over body sodium (Na⁺) balance.
 - If there are no signs of haemodynamic compromise, use a slow infusion of normal saline (0.9%) to keep the IV line patent and for maintenance fluids.
 - Use compatible blood when it is ready (give 1U/h or stat if comorbid conditions allow) until the volume is restored or CVP 5–10cm. If the rate of bleeding is slow, packed cells are preferred. If there is massive haemorrhage, ask for ‘O’-negative blood which may be given without cross-matching. Save serum for retrospective cross-match.
 - Consider clotting product ± *platelets* if ≥4U of RBCs given (or if the patient is stable; can be guided by laboratory results).
- *Monitor urine output*, and catheterize if there are signs of haemodynamic compromise. Aim for >30mL/h or 0.5–1mL/kg. Prompt resuscitation should restore urine output (see oliguria; ➡ Acute kidney injury 2, pp. 294–5).
- *Watch for the usual signs of overload* (raised JVP or CVP, pulmonary oedema, peripheral oedema). Too rapid transfusion may precipitate pulmonary oedema.
- *Commence IV PPI*: re-bleeding occurs in ~20% of patients after endoscopic treatment of bleeding ulcers. IV PPI infusion decreases the risk of re-bleeding from >20% to ~7%. It also reduces the need for surgery and repeated endoscopic treatment. Many centres use IV omeprazole or pantoprazole (80mg IV, followed by 8mg/h for

72h post-endoscopy).³ NICE guidelines do not advocate IV PPI prior to endoscopy, as there is no evidence this will reduce mortality or morbidity. However, many gastroenterologists do still prescribe IV PPI in patients with significant GI bleeding.

- Keep the patient NBM for endoscopy for 6–8h.

NB NICE guidelines³ on the management of upper gastrointestinal bleeding do not advocate the prescription of IV PPI prior to endoscopic therapy. However, many clinicians still prescribe omeprazole or pantoprazole 80mg IV bd prior to endoscopy.

Box 3.1 Management key points: initial management of upper GI bleed

- Protect the airway: position the patient on the side.
- IV access: two large-bore (14G–16G) cannulae. Insert a central line if peripheral access is difficult.
- G&S and cross-match 4–8U.
- IV fluids: if haemodynamically compromised, initially give 500mL to 1L of crystalloids over 1h, then crystalloids, and continue until compatible blood is available.
 - If there is massive haemorrhage: give 'O'-negative blood.
 - If there are no signs of haemodynamic compromise: give slow infusion of 0.9% saline to keep the IV line patent and for maintenance fluids.
 - Consider clotting product $\pm$ platelets if ≥ 4 U of RBCs given.
- Consider central line insertion and CVP monitoring in high-risk or haemodynamically unstable patients.
- Commence IV PPI infusion (80mg IV, followed by 8mg/h, 72h) after endoscopy in patients who required ulcer haemostasis (see note above for use of PPI pre-endoscopy).
- Monitor HR, BP, urine output, and CVP (if appropriate).
- Keep the patient NBM for endoscopy.

For variceal bleeding, see  Variceal haemorrhage: medical management, p. 236–7.

References

3. National Institute for Health and Care Excellence (2012). *Acute upper gastrointestinal bleeding in over 16s: management*. Clinical guideline [CG141].  <https://www.nice.org.uk/Guidance/cg141>

Peptic ulcer disease

Bleeding peptic ulcers form the mainstay (~50%) of upper GI bleeding—one-third of these have been taking an NSAID. Patients may give a history of epigastric distress relieved by food, but often there is no prior history.

- **Endoscopy:** allows the bleeding site to be visualized. Identification of the bleeding vessel or adherent clot has prognostic significance—>80% of these patients will re-bleed, cf. <5% without these stigmata.
 - The bleeding point may be treated endoscopically by electrocoagulation, adrenaline injection, or application of endoclips, heat probe, or laser photocoagulation.
 - Keep the patient NBM for 6–8h post-endoscopy, in case repeat endoscopy or surgery is needed.
- **Indications for surgery:** see Box 3.2.
- **Medical management:**
 - Treat with PPI for 4–8 weeks.
 - Repeat endoscopy at 6–8 weeks for all gastric ulcers to check the lesion has healed.
 - A biopsy should be taken at endoscopy for urease testing for *Helicobacter pylori*. Sensitivity affected by PPIs. Or use faecal antigen (Ag) testing. If positive, prescribe *H. pylori* eradication regimen (see BNF).
- **Prognosis:** overall mortality is <10%. Mortality is reduced by early surgery in high-risk patients.

Box 3.2 Relative indications for surgery

- Exsanguinating haemorrhage (too fast to replace).
- Profuse bleeding:
 - >6U of blood in initial resuscitation.
 - Continued bleeding at >1U per 8h.
 - Persistent hypotension.
- Re-bleed in hospital.
- Failed endoscopic therapy.
- Re-bleed after endoscopic therapy in patients >65 years.
- Lesions which are at high risk of re-bleeding, e.g. posterior duodenal ulcer (DU) with visible vessel or giant gastric ulcer.
- Special situations, e.g. patients with a rare blood group or patients refusing blood transfusion, should be explored earlier.

Erosive gastritis/oesophagitis

These generally present as relatively minor bleeds but may be significant. Represent ~15% of upper GI bleeds and are associated with prior use of aspirin or other NSAIDs in previously fit patients, or 'stress' in the critically ill patient (e.g. patients on ITU).

- *Management:* at endoscopy, there is commonly a generalized ooze of blood from the inflamed mucosa. Initial management is as before (see Box 3.1).
- Give PPI or sucralfate 1–2g qds PO or via an NG tube.
- PPIs are better than H₂-antagonists in healing oesophagitis and oesophageal ulcers.
- Correct any clotting disorder.
- If the lesions are too diffuse and bleeding continues, partial gastric resection may be necessary.
- *Prognosis:* <5% of patients with haemorrhagic gastritis require surgery. Overall mortality is <10%.

Variceal haemorrhage: medical management

Oesophageal and gastric varices develop with portal hypertension of whatever cause. Bleeding from varices is typically vigorous and difficult to control, and often occurs in the setting of abnormal clotting, thrombocytopenia, and sepsis.

Diagnosis

History and physical examination may raise the suspicion of a variceal source of bleeding, but ~30% of cirrhotics have a non-variceal source of bleeding. The most reliable method is upper GI endoscopy, which should be performed as soon as is feasible. Bleeding may occur from either gastric or oesophageal varices, or rarely portal hypertensive gastropathy.

Medical management

(See Box 3.3.)

- Initial resuscitation is as described under  Acute upper GI bleeding 2, pp. 230–1.
- Transfuse with blood, FFP, and platelets, as necessary, according to haematological parameters, to try to stop the bleeding. Give vitamin K 10mg IV once only to exclude vitamin K deficiency. Avoid overtransfusion (may increase the risk of rebleeding).
- *Antibiotics*: take blood, urine, and ascitic fluid for culture and microscopy. Start broad-spectrum antibiotics. Several studies have shown that variceal bleeding is associated with sepsis and that antibiotics also reduce re-bleeding rates. Commence a third-generation cephalosporin or ciprofloxacin and amoxicillin. Treat for 5 days.
- *Terlipressin*: (2mg initially, and then 1–2mg every 4–6h, for up to 72h) is effective in controlling variceal bleeding by causing splanchnic vasoconstriction (relative reduction in mortality of ~34%). Avoid high doses (2mg), if possible. Serious side effects occur in 4% and include cardiac ischaemia, peripheral vasoconstriction (which may produce significant hypertension), and skin and splanchnic ischaemia. *Octreotide* is a synthetic analogue of somatostatin. A Cochrane review found that octreotide had no effect on mortality and had a minimal effect on transfusion requirements.⁴ It is not recommended.
- *Band ligation* of varices: is most commonly used and is safer than injection sclerotherapy. It should be repeated at 2-weekly intervals until the varices have been obliterated.
- *Endoscopic injection*: of sclerosant into the varices or para-variceal can control the bleeding acutely. Side effects (serious in 7%) include retrosternal pain and fever immediately post-injection, mucosal ulceration, late oesophageal strictures, and PE. Gastric varices should be injected with cyanoacrylate glue.
- *Balloon tamponade*: a Sengstaken–Blakemore tube may be inserted ( Insertion of Sengstaken–Blakemore tube, p. 844), with inflation of the gastric balloon *ONLY*. This should not be left in place for >12h, as ischaemic ulceration may occur. Apply 1kg traction to compress the gastro-oesophageal junction and reduce blood flow to the varices.

- *Liver failure regimen* (☞ ‘Acute-on-chronic’ liver failure, p. 280): give lactulose 10–15mL tds PO or via an NG tube to prevent encephalopathy. In alcoholics, give thiamine and multivitamins. Use phosphate enemas for patients with severe encephalopathy.

Box 3.3 Management key points: variceal haemorrhage

- Initial resuscitation (see Box 3.1): transfuse with blood, FFP, and platelets, as necessary.
- Vitamin K (10mg IV, once).
- Prophylactic antibiotics: a third-generation cephalosporin (e.g. ceftriaxone) or ciprofloxacin and amoxicillin (for 5 days).
- Terlipressin (2mg initially, and then 1–2mg every 4–6h, for up to 72h).
- Oesophagogastroduodenoscopy (OGD): band ligation or sclerotherapy.
- If bleeding is not controlled, balloon tamponade (e.g. a Sengstaken–Blakemore or Linton tube) may be used to temporarily stabilize the patient, so that more definitive treatment [transvenous intrahepatic portosystemic shunting (TIPS) or surgery] can be instituted. These tubes should only be used in settings in which experienced staff are available.
- Some centres are now using Danis stents (a metal stent that directly compresses the varices to stop bleeding).

References

4. Ioannou GN, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. *Cochrane Database Syst Rev* 2003;1:CD002147. ☞ <http://www.cochrane.org/reviews/en/ab002147.html>

Variceal haemorrhage: further management

Radiological management

TIPS is available in specialized units. Using a jugular or femoral approach, the hepatic veins are cannulated and an expandable stent is placed between the hepatic veins (low pressure) and the portal venous system (high pressure). The portal pressure should be decompressed to below 12mmHg.

Surgical management

This has been largely superseded by TIPS.

- *Emergency porto-caval shunting* is effective in controlling the bleed (>95%) but has a high operative mortality (>50%) and does not influence long-term survival. Few surgeons can do this now.
- *Oesophageal transection* is never used now but remains an option.

Danis stent

Some centres have started using self-expanding, removable metal stents to compress bleeding oesophageal varices. The stent is normally inserted with the help of an endoscope (but can be inserted without). It is removed after 2 weeks. Further procedures, such as TIPS or surgery, may be carried out to reduce the risk of further bleeds.

Prognosis

- Overall mortality is 30%. This is highest in those with severe liver disease (Child–Pugh grade C; see Table 3.3).
- Success rates for cessation of acute bleeding varices are:
 - Injection sclerotherapy or banding: ~70–85%.
 - Balloon tamponade: ~80%.
 - Terlipressin: ~70%.

Long-term management

- *Band ligation* every 2 weeks until variceal obliteration more rapidly (39 days versus 72 days).
- *Injection sclerotherapy* is rarely used now.
- *Propranolol* (up to 80mg tds; aim for a 30–40% reduction in resting HR, but confirm reduction of portal pressure by measurement of wedged hepatic venous pressure gradient) reduces the rate of re-bleeding from varices and portal hypertensive gastropathy. It has not been shown to decrease mortality.
- *TIPS* or shunt procedures provide a more definite cure, and bleeding tends to recur only when the shunt blocks, but there is an ↑ incidence of chronic hepatic encephalopathy. It is very effective.

Table 3.3 Child–Pugh score*

Clinical or biochemical variable	Points scored		
	1	2	3
Encephalopathy grade	None	1–2	3–4
Ascites	Absent	Mild	Moderate to severe
Bilirubin (micromol/L)	<35	36–60	>60
Albumin (g/L)	>35	28–35	<28
PT (seconds prolonged)	1–4	4–6	>6
The Child–Pugh scoring system is a very effective way to get an index of the severity of liver disease in patients with cirrhosis. It is not directly applicable to patients with primary biliary cirrhosis or sclerosing cholangitis.			
Child–Pugh A:	Score ≤6		
Child–Pugh B:	Score 7–9		
Child–Pugh C:	Score ≥10		

* Reproduced from Pugh RNH et al., 'Transection of the oesophagus for bleeding oesophageal varices', *British Journal of Surgery*, 60(8), pp. 646–9, with permission from John Wiley and Sons. Copyright © 1973 British Journal of Surgery Society Ltd.

Mallory–Weiss tear

This is a tear in the mucosa at the gastro-oesophageal junction following severe retching and is particularly common following large bouts of alcohol. The vomit is normal initially and becomes bright red.

Management

- Most stop bleeding spontaneously.
- Tamponade with a Sengstaken–Blakemore tube may be used.
- Surgical oversewing of bleeding point or selective arteriography and embolization of the feeding artery may be necessary.

Acute gastroenteritis: assessment

Food poisoning is an acute attack of abdominal pain, diarrhoea $\pm$ vomiting 1–40h after ingesting contaminated foodstuffs and lasting 1–7 days. With the exception of an acute attack of inflammatory bowel disease (IBD) and mesenteric ischaemia (➡ Inflammatory bowel disease 1, p. 254), the majority of acute-onset diarrhoea has an infective aetiology.

Differential diagnosis of acute diarrhoea

Common

- Gastroenteritis (bacterial, viral, protozoal).
- *Clostridium difficile* diarrhoea (pseudomembranous colitis).
- IBD.
- Food intolerance/allergy (e.g. lactase deficiency).
- Drugs (see Box 3.7).

Less common

- Coeliac disease.
- Tumour (benign or malignant).
- Carcinoid syndrome.
- Bacterial overgrowth.
- Irritable bowel syndrome.
- Pancreatic insufficiency.
- Bile salt enteropathy.
- Hyperthyroidism.
- Autonomic neuropathy.
- Ischaemic bowel.

Presenting features

Ask specifically about:

- Recent eating habits, especially restaurants and food prepared by caterers. Anyone else (family/friends) with similar symptoms?
- Time interval between eating any suspicious substance and onset of symptoms. Early onset of vomiting or diarrhoea (6–12h) suggests ingestion of preformed toxin (e.g. *Staphylococcus* exotoxin). Enterotoxin-producing organisms may take 1–3 days to produce symptoms.
- Recent travel (enterotoxigenic *Escherichia coli*, *Salmonella*, *Giardia*, or amoeba)? Recent medication? Any antibiotics (*C. difficile*)?
- Past medical history, e.g. gastric surgery or immunosuppression (drugs or HIV).
- Oro-anal intercourse increases the risk of amoebiasis, giardiasis, and shigellosis. Insertive anal intercourse increases the risk of rectal syphilis, rectal gonorrhoea, *Chlamydia trachomatis*, and herpes simplex virus (HSV) infection of the rectum and perianal area (diarrhoea in HIV-infected patients is discussed under ➡ Gastrointestinal presentations in HIV-positive patients: assessment, p. 528).
- The gross appearance of the diarrhoea may help: frankly bloody stool—*Campylobacter* or *Shigella*; watery, ‘rice-water stool’—classically secretory diarrhoea due to cholera, enterotoxigenic *E. coli*, or neuroendocrine tumours. Typhoid classically associated with constipation when typically presents with fever, though early phase (often prodromal) may have greenish ‘pea-soup’ diarrhoea.
- Abdominal pain may be present: usually cramp-like or tenesmus.
- Fever: common with severe bacterial diarrhoea and acute exacerbations of CD or ulcerative colitis (UC).

Bacterial gastroenteritis

Salmonella spp.

May produce acute gastroenteritis (e.g. *S. enteritidis*, ~70–80% of cases), enteric fever (*S. typhi* and *S. typhimurium*; ➡ Enteric fever (typhoid), pp. 490–1), or asymptomatic carriage. Acute gastroenteritis often occurs in epidemics and is derived from poultry, eggs, or egg products, and occasionally pets (terrapins).

- **Symptoms:** 8–48h after ingestion, with headache, vomiting (worse than either *Shigella* or *Campylobacter*), fever, and diarrhoea lasting 2–4 days (rarely bloody, with mucus). Reactive arthritis may occur (in HLA-B27 +ve). Enteric fever (➡ Enteric fever (typhoid), pp. 490–1).
- **Management:** usually self-limiting after 2–5 days, and treatment is supportive for most cases. Some antibiotics can prolong carriage of the illness and make clinical relapse more likely.

Clostridium perfringens (type A)

Fifteen to 25% of cases of bacterial food poisoning. Spores are heat-resistant and may germinate during reheating or slow cooking of meats. Enterotoxin is released when sporulation occurs in the intestine. Incubation 8–22h.

- **Symptoms:** diarrhoea, abdominal pain, nausea (rare to get vomiting). No fever. Lasts 12–24h.
- **Management:** supportive.

Campylobacter

Campylobacter infections are common (5–10% of patients with acute diarrhoea). The incubation period is 3–7 days; symptoms last for 1–2 weeks. Presentation often follows eating contaminated poultry.

- **Symptoms:** flu-like illness, followed by headache, myalgia, abdominal pain (continuous, then colicky), diarrhoea, and rectal bleeding occasionally. Rarely complicated by reactive arthritis (1–2%), GBS, or Reiter's syndrome.
- **Management:** usually self-limiting, <5 days. Treatment comprises either erythromycin or tetracycline. Anti-diarrhoeals are contraindicated.

Staphylococcus aureus

(2–5% of cases) Can multiply at room temperature in foods rich in carbohydrates and salt (dairy products, cold meats, mayonnaise). A heat-stable exotoxin produces nausea, vomiting, and diarrhoea 1–6h after ingestion. Fever is uncommon. Treatment is supportive.

Bacillus cereus

Associated with slow-cooking foods and reheated rice (fast-food take-aways). It produces a toxin that causes vomiting within 1–5h, and diarrhoea 8–16h later. Treatment is supportive.

Vibrio parahaemolyticus

Produces epigastric pain (cf. those above), diarrhoea, vomiting, and fever 12–18h after ingestion of raw seafood (shellfish). May last up to 5 days. *Vibrio cholerae* is uncommon in western nations. It produces profuse secretory diarrhoea. The disease is usually self-limiting (5–7 days), but tetracyclines may be used.

Yersinia enterocolitica

Incubation period is 4–10 days after contact with infected animals, water, or ice cream.

- *Symptoms*: diarrhoea (80%), abdominal pain (80%), fever (40%), bloody stool (10%), mesenteric adenitis, lymphadenopathy, reactive arthritis. Diagnosed by serology, rather than culture.
- *Management*: supportive.

Shiga toxin-producing *E. coli* (e.g. O157:H7)

Infection is usually from contaminated meat/burgers. The incubation period is ~5 days. Stools become bloody over 24–48h, secondary to diffuse colitis. Most patients resolve over 5–7 days without treatment. However, some patients, especially children, may go on to develop haemolytic uraemic syndrome (HUS), with tiredness, microangiopathic anaemia, thrombocytopenia, renal failure, and encephalopathy. Most recover with supportive care. Antibiotics are contraindicated, as some antibiotics increase shiga toxin release and exacerbate or cause the development of HUS.

Viral gastroenteritis

In addition to diarrhoea, URTI-like symptoms, abdominal cramps, headache, and fever may occur. High frequency of vomiting. The causative agent is usually not found, but many viruses are implicated (e.g. echovirus, Norwalk virus, rotavirus, and adenoviruses). Self-limiting illness (3–5 days).

Management

Oral fluids and restricting solid foods and dairy product intake usually suffice. If <65 years old, and volume-deplete or moderate to severe diarrhoea, consider 1–2 days of loperamide. If excessive vomiting, treat with antiemetics (e.g. prochlorperazine).

Clostridium difficile

Patients with *C. difficile* infection can be asymptomatic (carrier) or present with diarrhoea and toxic megacolon at the extreme. Caused by two necrolytic toxins (A and B) produced by *C. difficile*. It is the most common cause of hospital-acquired diarrhoea. Infection typically follows antibiotic therapy. Diarrhoea may occur during or up to 4 weeks following cessation of treatment.

Symptoms

Diarrhoea is usually profuse and watery, and may be bloody in ~5% of patients. It is commonly associated with abdominal cramps and tenderness, fever ($>38.5^{\circ}\text{C}$ when severe), and an elevated WCC ($>30 \times 10^9/\text{L}$).

Diagnosis

Diagnosis is based on the detection of *C. difficile* toxin or toxin gene in stool. Culture of the organism itself is unhelpful; ~5% of healthy adults carry the organism. Sigmoidoscopy is not diagnostic but may show mucosal inflammation, together with multiple yellow plaques (pseudomembranous colitis), which is highly suggestive and should prompt laboratory investigation. Laboratory testing consists of checking for the antigen and toxin. If the antigen is negative, diarrhoea is highly unlikely to be due to *C. difficile* infection. For other combinations, see Management section below.

Management

- General considerations: rehydrate and correct electrolyte abnormalities. Complications include toxic megacolon and colonic perforation. Faecal transplantation from healthy individuals has shown promising results in clinical trials (80% cure rate on first transplant, with further 80% cure rate if the first transplant is unsuccessful).
- Antigen positive and toxin positive: isolate and barrier-nurse. Mild disease responds to oral metronidazole (400mg tds). Oral vancomycin 250mg qds for 7–14 days is an alternative. Severe disease requires oral vancomycin as first line, and addition of IV metronidazole if not improving. Fidaxomicin may be considered in patients who cannot tolerate vancomycin, although more data are needed.
- Antigen positive, toxin negative: isolate if symptomatic; review (and stop, if possible) antibiotics; stop PPIs and laxatives, if possible. If high risk (age >65 , on antibiotics/PPI, antibiotics within last 30 days, recurrent hospital admissions), consider oral metronidazole and/or vancomycin.

Giardiasis

Giardia lamblia is transmitted by the faeco-oral route. Risk factors include recent travel, immunosuppression, homosexuality, and achlorhydria.

Symptoms

More chronic diarrhoeal illness with epigastric discomfort due to duodenal infestation. Malaise, bloating, flatulence, and occasionally malabsorption occur. Diagnosis is by stool microscopy for cysts or trophozoites or by duodenal aspiration. If negative, consider blind therapeutic trial.

Management

Metronidazole is the treatment of choice—2g daily for 3 days or 400mg tds PO for 5 days. Alternatives include tinidazole (2g, single dose) or mepacrine hydrochloride 100mg tds for 5–7 days. Lactose intolerance post-infection may persist for up to 6 weeks.

Travellers' diarrhoea

Travel through developing countries is commonly associated with self-limiting acute diarrhoeal illness transmitted through food and water. The most frequent pathogen is enterotoxigenic *E. coli* (40% of cases) (see Box 3.5). The illness lasts 3–5 days, with nausea, watery diarrhoea, and abdominal cramps. Oral rehydration is usually sufficient. Antimotility agents (e.g. loperamide) may be used with caution. Antibiotic treatment (ciprofloxacin 500mg bd) may help patients with more protracted illness. Alternatives include doxycycline or co-trimoxazole (for travellers from South East Asia, azithromycin may be a better choice of empiric therapy due to high quinolone resistance). Diarrhoea that persists for >7 days requires further investigation, including stool microscopy and culture, serology, sigmoidoscopy, and biopsy (see Box 3.6). A 3- to 5-day course of a broad-spectrum antibiotic, such as ciprofloxacin, may terminate the illness. For common drugs that may cause acute diarrhoea, see Box 3.7.

Box 3.5 Causes of travellers' diarrhoea

Bacterial

- Enterotoxigenic *E. coli* (40%).
- *Shigella* and enteroinvasive *E. coli* (10%).
- *Salmonella* (5%).
- *Campylobacter* (3%).
- *Aeromonas/Plesiomonas* (5%).
- *V. parahaemolyticus* (1%).

Not-identified (22%)

Viruses (10%)

- Norwalk.
- Rotavirus.

Protozoa (4%)

- *Giardia*.
- *Entamoeba*.
- *Cryptosporidium*.
- *Microsporidium*.

Box 3.6 Causes of persistent diarrhoea in travellers

Protozoa

- *G. lamblia*.
- *Entamoeba histolytica*.
- *Cyclospora cayetanensis*.

Bacteria

- *Salmonella*.
- *Campylobacter*.

Helminths

- *Strongyloides*.
- Colonic schistosomiasis (rare).

Box 3.7 Common drugs that may cause acute diarrhoea

- | | | |
|--------------------------------------|-----------------------|----------------|
| • Laxatives. | • Colchicine. | • Propranolol. |
| • Antacid (Mg^{2+} , Ca^{2+}). | • Quinidine. | • Aspirin. |
| • Lactulose. | • Digitalis. | • NSAIDs. |
| • Diuretics therapy. | • Theophyllines. | • Cytotoxic. |
| • Antibiotics. | • Cholinergic agents. | • Captopril. |

NB There are many drugs other than those listed here that can cause diarrhoea.

Bloody diarrhoea

Causes

- Acute infectious colitis:
 - Bacillary dysentery (*Shigella* spp.).
 - Salmonellosis (☞ Enteric fever (typhoid), pp. 490–1).
 - *Campylobacter* (☞ Bacterial gastroenteritis, pp. 244–5).
 - Amoebic dysentery.
 - Haemorrhagic colitis (shiga-like toxin-producing *E. coli*).
 - Pseudomembranous colitis (☞ *Clostridium difficile*, p. 247).
 - Ischaemic colitis.
 - Lymphogranuloma venereum (LGV).
- IBD (UC or CD).

Presenting features

- Ask about the duration of symptoms and recent eating habits. Others affected? Recent travel (enterotoxigenic *E. coli*, *Salmonella*, or amoeba)? Any antibiotics (*C. difficile*)?
- The gross appearance of the stool may help. IBD may result in rectal bleeding (fresh red blood) in patients with disease largely confined to the rectum and sigmoid colon. Diffuse disease tends to be associated with diarrhoea. Infectious colitis results in frankly bloody stool (*Campylobacter* or *Shigella*).
- Abdominal pain may be present: usually cramp-like or tenesmus.
- Vomiting is uncommon in acute IBD.
- Systemic features, such as general malaise and lethargy, dehydration with electrolyte imbalance, or fever, are seen with severe bacterial diarrhoeas and acute exacerbations of CD or UC. Skin, joints, and eyes may be involved either in IBD or following an acute infection.
- Previous altered bowel habit, weight loss, smoking history, vascular disease (mesenteric infarction), and mesenteric angina may be relevant.

Examination

Look for:

- Fever, signs of dehydration (tachycardia, postural hypotension), and abdominal distension. Abdominal tenderness or rebound over affected colon (IBD) may indicate colonic dilatation or perforation. An abdominal mass may indicate a tumour or an inflammatory mass.
- Mouth ulcers and perianal disease are common in active IBD.
- Erythema nodosum and pyoderma gangrenosum occur in IBD; *Yersinia* may produce erythema nodosum. Rose spots indicate typhoid fever.
- Joint involvement (often an asymmetrical, non-deforming synovitis, involving large joints of the lower limbs) may occur in active IBD, but also in infectious colitis (e.g. *Campylobacter*, *Yersinia*).
- Uveitis is associated with both IBD and acute infectious colitis.

Investigations

The priority is to exclude any infectious cause for the bloody diarrhoea and to monitor for complications.

- *Blood tests*: FBC, U&Es, LFTs, CRP, ESR, coagulation studies.
- *Microbiology*: stool MC&S, blood cultures, *C. difficile* toxin, ova, cysts, and parasites.
- *Sigmoidoscopy biopsy*: may help to distinguish between acute infectious colitis and IBD (↑ risk of perforation during colonoscopy). Appearance of pseudomembranes (a yellow layer of exudate resembling a membrane) indicates possible *C. difficile*.
- *Imaging*: plain abdominal X-ray (AXR) may help monitor colonic dilatation. Contrast studies are contraindicated acutely.

Practice points

- Always test for *C. difficile* in patients with new-onset bloody diarrhoea.
- In unexplained extreme leucocytosis (e.g. WCC >35 000), consider *C. difficile*.

Bacterial dysentery

This is due to infection with *Shigella* (*S. dysenteriae*, *S. flexneri*, *S. boydii*, *S. sonnei*), *Salmonella*, *Campylobacter*, or some *Shigella*-like *E. coli* (O157:H7). Transmitted by the faeco-oral route, and clusters of cases are often found.

Symptoms

- It causes mild diarrhoea to a severe systemic illness between 1–7 days following exposure.
- Fever (usually resolves in 3–4 days).
- Abdominal cramps with tenesmus.
- Watery diarrhoea $\pm$ nausea and vomiting (resolves by day 7). Bloody diarrhoea occurs later (after 24–72h) due to invasion of the mucosa.
- Diagnosed by stool culture. *E. coli* infections may be complicated by HUS.

Management

- Patients may require IV fluid replacement.
- Antibiotics should be reserved for the most severe cases. Ciprofloxacin (500mg PO bd for 7–10 days) is usually effective, but in resistant cases, co-trimoxazole or ciprofloxacin may be used.
- Antimotility agents, such as loperamide and codeine, are contraindicated, as they prolong carriage and worsen symptoms.

Amoebic dysentery

E. histolytica can produce intermittent diarrhoea or a more severe illness that resembles IBD. There is an ↑ risk in homosexuals and in those with recent travel to third-world countries. It is transmitted by the faeco-oral route.

Diagnosis is through serology or antigen testing, together with identification of the parasite in stool or extraintestinal sites (such as liver abscess pus).

Symptoms

- Diarrhoea or loose stool ($\pm$ blood), abdominal discomfort, mild fever. In severe cases, liver abscess.
- Fulminant attacks present abruptly with high fever, cramping abdominal pain, and profuse bloody diarrhoea.
- Marked abdominal tenderness and tenesmus are present.
- Diagnosis is made by identifying amoebic cysts on stool microscopy.
- May be complicated by the development of amoebic liver abscess.

Treatment

- Aimed at replacement of fluid, electrolytes, and blood loss, and eradication of the organism.
- In acute invasive intestinal amoebiasis, oral metronidazole (800mg tds for 5–10 days) is the treatment of choice. Tinidazole (2g daily for 2–3 days) is also effective. This should be followed with oral diloxanide furoate (500mg tds for 10 days) to destroy gut cysts.
- Metronidazole (or tinidazole) and diloxanide furoate are also effective for liver abscesses, and US-guided aspiration may help improve penetration of the drugs and shorten the illness.
- Diloxanide furoate is the treatment of choice for asymptomatic patients with *E. histolytica* cysts in the stool, as metronidazole and tinidazole are relatively ineffective.

Inflammatory bowel disease 1

IBD includes CD and UC. CD is a chronic inflammatory disease of any part of the gastrointestinal tract (GIT), characterized by granulomatous inflammation. UC is a chronic inflammatory disease of the colon. It always affects the rectum and extends proximally to a variable extent of the colon. The aetiology of IBD is poorly understood.

Ulcerative colitis

Presentation

- Gradual onset of progressively more severe symptoms.
- Diarrhoea is dependent on disease activity and extent. Nocturnal diarrhoea and urgency are common symptoms of severe UC.
- Mucus and frank pus, or blood, are often mixed in with the stool.
- Occasionally abdominal pain (not a prominent feature, though lower abdominal cramping pains relieved by defecation is common; severe abdominal pain suggests a severe attack with acute dilatation or perforation, or ischaemic colitis).
- Urgency and tenesmus.
- In severe disease there is severe (>6 motions/day) and nocturnal diarrhoea, anorexia, and weight loss. Blood may be altered in colour.
- Aphthous ulcers (also present in CD).
- Ask about recent cessation of smoking (precipitant).

Examination

Look for fever, signs of dehydration (tachycardia, postural hypotension), and abdominal distension. *Abdominal tenderness* $\pm$ rebound may indicate colonic dilatation or perforation. This may be masked if the patient is on steroids. An abdominal mass may indicate a tumour or an inflammatory mass. Toxic megacolon (>6cm on AXR) can be life-threatening. *Systemic features*: examine for extraintestinal manifestations (see Box 3.8).

Crohn's disease

Presentation

- Diarrhoea (80%).
- Abdominal pain (50%) (colic and vomiting suggest ileal disease).
- Weight loss (70%) and fever (40%).
- Obstructive symptoms (colic, vomiting).
- Rectal bleeding (50%) (more common in colonic disease but is present in 50% with ileal disease; colonic disease is associated with perianal disease in 30%).
- Extraintestinal manifestations such as erythema nodosum (5–10%), arthropathy (10%), or eye complications (5%) (see Box 3.9).
- Symptoms of anaemia (iron, B₁₂, or folate deficiency) or nutritional deficiencies.

Examination

Examine nutritional status and for evidence of malabsorption. Examine for evidence of intestinal obstruction (strictures). Fistulae may occur between the bowel and other organs (bladder, vagina). Toxic megacolon is much rarer than in UC. Bloody diarrhoea is occasionally massive.

Box 3.8 Extraintestinal manifestations of UC*Related to disease activity*

- Aphthous ulcers.
- Fatty liver.
- Erythema nodosum.
- Peripheral arthropathy.
- Episcleritis.
- $\pm$ pyoderma gangrenosum.
- $\pm$ anterior uveitis.

Unrelated to disease activity

- Sacroiliitis.
- Ankylosing spondylitis.
- Primary sclerosing cholangitis (PSC).
- Cholangiocarcinoma (usually with PSC).

Box 3.9 Extraintestinal manifestations of Crohn's disease*Related to disease activity*

- Aphthous ulceration (20%).
- Erythema nodosum (5%).
- Pyoderma gangrenosum (0.5%).
- Acute arthropathy (8%).
- Eye complications (5%):
 - Conjunctivitis.
 - Episcleritis.
 - Uveitis.

Unrelated to disease activity

- Sacroiliitis (15%).
- Ankylosing spondylitis (4%).
- Liver disease (5%):
 - Gallstones common.
 - Chronic active hepatitis (2%).
 - Cirrhosis (2%).
 - Fatty change (5%).

Inflammatory bowel disease 2

Markers of a severe attack of IBD

- Truelove and Witts criteria for severe UC:
 - >6 bloody stools/day AND any one of:
 - Pyrexia ($>37.8^{\circ}\text{C}$) or tachycardia ($>90\text{bpm}$) or Hb $<10.5\text{g/dL}$ or ESR $>30\text{mm/h}$.
- Other indicators include:
 - Albumin $<30\text{g/L}$.
 - Toxic dilatation (colon $>6\text{cm}$).

These symptoms, signs, or findings also indicate severe CD. However, it should be noted that severe CD may be present in the absence of any of the listed markers.

Investigations

- *Blood tests*: anaemia may be present if the colitis is acute and florid (chronic iron deficiency anaemia is also common). A severe iron deficiency picture may be observed. $\uparrow$ WCC (neutrophilia) and $\uparrow$ platelets. $\downarrow$ K^+ may follow severe diarrhoea. There may also be an element of pre-renal dehydration. In severe colitis, albumin often falls to $20\text{--}30\text{g/L}$. ESR and CRP reflect disease activity and are useful to monitor therapy, though are often not elevated in distal (rectal) disease.
- *Stool culture and microscopy*: include *C. difficile* toxin.
- *Supine AXR $\pm$ erect CXR*: to look for wall thickening (moderate to severe) and mucosal oedema, with loss of haustration and colonic dilatation (more severe cases). Colonic diameter $>6\text{cm}$ indicates toxic dilatation, with risk of perforation. The extent of the disease can be indirectly assessed; distal colitis is often associated with proximal faecal loading. In the acute stages of a severe attack, abdominal films should be performed daily, or twice daily if there is borderline toxic dilatation. Free air under the diaphragm on an erect CXR indicates perforation. CT scan is useful to confirm visceral perforation, especially if the patient is in pain.
- *MRI*: is helpful in investigating the small bowel. There is a role for *US*, especially for investigating terminal ileal inflammation or right iliac fossa collection (however, *US* is very operator-dependent).
- *Sigmoidoscopy $\pm$ colonoscopy*: perform sigmoidoscopy within 24h of admission in severe cases. Bowel preparation is unnecessary and may cause reddening of the mucosa. Flexible sigmoidoscopy has a lower risk of bacteraemia and is easier than rigid sigmoidoscopy. Non-specific findings, such as hyperaemia and contact or spontaneous bleeding, are common. Ulceration suggests acute and severe disease; pseudopolyps and atrophy of the bowel mucosa indicate chronic UC. Biopsies should be taken and analysed for CMV co-infection ($\uparrow$ risk due to immunosuppression).

Inflammatory bowel disease 3

Management

- Admit under a specialist gastroenterology team.
- Rehydrate the patient with IV fluids, and correct any electrolyte imbalance (hypokalaemia, in particular). Inform and discuss the patient with surgical colleagues, especially if moderate to severe.
- *LMWH*: prophylactic dose of LMWH—severe IBD results in procoagulant state with ↑ risk DVT ± PE.
- The differential diagnosis is wide (see Box 3.10). Exclude infectious colitis (normal stool microscopy and culture) and systemic infections as far as possible.
- Avoid antimotility and opiate drugs (such as loperamide and codeine) and antispasmodics, as they cause proximal constipation and may precipitate paralytic ileus and megacolon.
- *Corticosteroids*: mild to moderate attacks of UC may respond to rectal steroids (e.g. Predfoam® or Predsol® enema, 20mg 1–2 times daily), especially if the disease is confined to the rectum. However, severe attacks require IV steroids (hydrocortisone 100mg qds IV) until remission is achieved. Severe CD should be treated with IV steroids (hydrocortisone 100mg qds IV). Where no improvement on IV steroids after 3 days, consider IV ciclosporin or infliximab as rescue therapy.
- *Aminosalicylates*: in patients with UC, mesalazine should be started (800mg bd or tds PO) ± mesalazine foam enema [1g od per rectum (PR)], in addition to steroids—they help induce, and maintain, remission after steroids are tailed off. Use mesalazine for ileal CD.
- *Elemental diets*: are as effective as steroids for the treatment of CD. However, it is difficult to get patients to comply.
- *Other agents*: azathioprine (2mg/kg daily) has no role in acute attacks (8–12 weeks to take effect), but useful for maintenance of remission. Methotrexate has no role in acute attacks of UC, but there is variable success with CD. Two trials have reported nicotine patches significantly improve symptoms and help to induce remission of UC.
- *Antibiotics*: there is no evidence that broad-spectrum antibiotics are useful in UC. Metronidazole is useful in the treatment of perianal Crohn's fistulae. Ciprofloxacin may also be useful in CD. Other antibiotics should only be used if specifically indicated and should be considered for patients developing toxic megacolon.
- *Infliximab*: is used for perianal and fistulating CD, as well as severe CD where other medical treatments have failed.
- *Nutrition*: there is no evidence for keeping the patient 'NBM'. However, low-residue and early institution of TPN may be of benefit, especially if the patient is likely to go to surgery (see Box 3.11). When the patient is recovering, stool-bulking agents (e.g. methylcellulose) may be used to adjust stool consistency.
- *Smoking*: encourage patients who smoke to stop, as this enhances remission rates in CD.

Indications for surgery

- In UC, failure of symptoms to resolve after 5 days of medical therapy is an indication for pan-proctocolectomy. A staged procedure (colectomy first) is recommended in this situation.
- Colonic perforation, uncontrollable bleeding, and fulminating disease require urgent proctocolectomy; ~30% of all patients with UC will require a colectomy at some stage.
- Toxic dilatation prior to treatment is not an indication for surgery (failure of the colonic diameter to decrease after 24h). The development of dilatation during treatment is an indication for surgery.
- Surgery in CD is not 'curative' and is only indicated for perforation, obstruction, abscess formation, and fistulae (enterocutaneous or enterovesical). There is a high recurrence rate after surgery.

Box 3.10 Differential diagnosis of inflammatory bowel disease

Bacteria

- *Shigella*.
- *Salmonella*.
- *E. coli*.
- *Campylobacter*.
- *C. difficile*.
- TB.
- *Gonococcus*.
- *Chlamydia*.
- *Yersinia*.

Parasites

- Amoebiasis.
- Schistosomiasis.

Miscellaneous

- Ischaemic colitis.
- Lymphoma.
- Trauma.
- Radiation colitis.

Box 3.11 Management key points: acute management of inflammatory colitis

- Admit under a specialist gastroenterology team.
- IV fluids: rehydrate the patient, and correct any electrolyte imbalance (e.g. hypokalaemia). Correct anaemia.
- Corticosteroids: IV hydrocortisone 100mg qds (+ rectal steroids in acute UC or CD with distal colonic disease).
- Prophylactic LMWH. Presence of bloody diarrhoea is not a contraindication, as these patients are in a hypercoagulable state and at ↑ risk of DVT.
- Metronidazole if patients with CD have temperature or focal tenderness. Also give in UC if concerned about possible bacterial infection.
- Avoid ant motility drugs, opiates, and antispasmodics (cause proximal constipation and may precipitate paralytic ileus and megacolon).
- Inform and discuss the patient with surgical colleagues.
- Flexible sigmoidoscopy within 24h, with CMV histology and immunostaining.
- Nutrition: low-residue and early institution of TPN may be of benefit, especially if the patient is likely to go to surgery.

Jaundice: assessment

Jaundice requires urgent investigation and diagnosis. It may herald the onset of severe hepatitis and acute liver ($\pm$ renal) failure (➡ Acute liver failure: assessment and investigations, pp. 276–7). It may indicate obstructive jaundice which can be complicated by cholangitis and septicaemia (➡ Biliary obstruction, pp. 272–3).

History

- Non-specific symptoms include anorexia, pruritus, malaise, lethargy, drowsiness, confusion, or coma. Dark urine and pale stools may be features of either obstructive jaundice or hepatitis.
- Colicky right upper quadrant (RUQ) pain, previous biliary colic, or known gallstones suggests biliary colic (➡ Biliary obstruction, pp. 272–3). Fever, rigors, abdominal pain, and fluctuating jaundice should raise the suspicion of cholangitis. Painless jaundice and weight loss suggest pancreatic malignancy.
- Take a detailed drug history, including over-the-counter (OTC), herbal, homeopathic, or proprietary preparations. Ask about use of paracetamol and alcohol.
- Risk factors for infectious hepatitis: blood transfusion, IV drugs, tattoos, being homosexual, travel, ethnic origin, ingestion of shellfish.

Examination

- Note the degree of jaundice, and look for stigmata of chronic liver disease (spider naevi or telangiectasia, palmar erythema, Dupuytren's contractures, etc.). Lymphadenopathy may reflect malignancy. Hepatic encephalopathy results in falling conscious level and liver flap.
- Note the BP and the diastolic carefully—it falls with liver failure. Oliguria or shock may occur with acute liver failure (➡ Acute liver failure: assessment and investigations, pp. 276–7). Examine for pleural effusions (may occur with ascites).
- Examine the abdomen for ascites, hepatomegaly, splenomegaly (portal hypertension or intravascular haemolysis), or masses.

Causes of jaundice

- Viral hepatitis.
- Alcoholic hepatitis $\pm$ cirrhosis.
- Drug-induced hepatitis (including paracetamol).
- End-stage cirrhosis (alcoholic, chronic viral hepatitis, haemochromatosis, Wilson's disease, cryptogenic cirrhosis, etc.).
- Haemolytic anaemia.
- Gilbert's syndrome (mild jaundice).
- Biliary obstruction (stones or turnover).
- Intrahepatic cholestasis, post-hepatic [primary biliary cirrhosis (PBC), PSC, sepsis, drugs].
- Autoimmune hepatitis.
- Ischaemic hepatitis.
- Sepsis.
- Leptospirosis.
- Malaria.

Urgent investigations for jaundice (on day of admission)

- *U&Es, LFTs* Exclude renal failure [including hepatorenal syndrome (HRS)];  Hepatorenal syndrome, pp. 308–9).
- *Glucose* DM is common in haemochromatosis or pancreatitis.
- *PT* ↑ in severe liver injury or DIC.
- *FBC* ↓ platelets (chronic liver disease, with hypersplenism secondary to cirrhosis).
- *Urinalysis* Absence of bilirubin in the urine in a jaundiced patient.
- *Septic screen* e.g. blood cultures, ascitic tap (microscopy and culture), if relevant.
- *CXR* Tumour or metastases, effusion associated with ascites.
- *USS* If unwell or septic, exclude biliary obstruction.
- *Paracetamol* If overdose is suspected or possible.

Non-urgent investigations for jaundice

- *Viral serology* Anti-hepatitis A virus (HAV) IgM, hepatitis B surface Ag (HbsAg) and anti-hepatitis B core (HBc), anti-hepatitis C virus (HCV), hepatitis E virus (HEV), ± EBV or CMV serology.
- *Immunology* ANA, anti-SM, anti-LK-1, anti-mitochondrial antibody (AMA), and immunoglobulins (Igs) [congenital adrenal hyperplasia (CAH), PBC], ANCA.
- *Ferritin, iron, transferrin* ↑ ferritin is seen in any acute illness but may indicate haemochromatosis (↑ in alcoholic liver hepatitis).
- *Wilson's disease* Further investigations may be required for Wilson's disease, depending on the patient's score on the international risk score for Wilson's disease.

Viral hepatitis

Hepatitis A, hepatitis B, or delta co-infection of hepatitis B virus (HBV) carriers can lead to acute hepatitis with jaundice. Acute hepatitis C can present with jaundice, but this is less usual. EBV infection frequently causes abnormal LFTs, including mild or moderate jaundice, and is often associated with splenomegaly and lymphadenopathy during the acute phase. Patients should be asked about IV drug use, recent tattoos, sexual contacts, and any family or contact history of jaundice or hepatitis. Consider CMV hepatitis in immunocompromised patients. Hepatitis E is usually self-limiting (can become chronic in immunocompromised patients).

- Prodromal 'flu-like' illness and very high transaminase (up to ~4000U/L), with a small increase in ALP activity.
- If there is no coagulopathy, encephalopathy, or renal failure, send the patient home, and await virology results. Arrange repeat LFTs and clotting at 2- to 3-day intervals, and see the results (but not necessarily the patient). See the patient again within a week. Instruct the patient and carers to return if increasingly unwell or drowsy.

Hepatitis A

Patients with acute hepatitis A (anti-HAV IgM positive) require no specific treatment, but all household and school contacts should be immunized with HAV vaccine $\pm$ normal human Ig^s (see Box 3.12 for details). Patients with acute hepatitis A may rarely develop acute liver failure, although the prognosis is relatively good (>80% survival) with conservative management. Acute hepatitis A may be associated with high fever (40°C).

Hepatitis B

HBsAg appears in serum 1–10 weeks after an acute exposure to hepatitis B and prior to the onset of symptoms or increased alanine transaminase (ALT). As HBsAg disappears from serum, HBsAb appears, and there may be a window period when both are negative. Detection of anti-HBc IgM is usually regarded as an indication of acute HBV infection; however, anti-HBc IgM may remain detectable up to 2 years after the acute infection, and anti-HBc may increase to detectable levels during exacerbations of chronic hepatitis B.

In the majority of patients who recover, HBsAg becomes undetectable after 4–6 months. Persistence of HBsAg for >6 months suggests chronic infection. The rate of progression from acute to chronic hepatitis B is <1–5% for adult-acquired infection. Patients with acute HBV do not require acute antiviral treatment. However, many clinicians treat patients with severe hepatitis (e.g. INR >1.5) or protracted symptoms or marked jaundice for >4 weeks after presentation, as well as those who are immunocompromised or have pre-existing liver disease, since this may reduce the likelihood of re-infection post-liver transplantation.

For HBsAg-positive patients, family and close contacts should be tested for HBsAg, HBsAb, and anti-HBc IgM. Prophylactic-specific hepatitis B immunoglobulin ('HBIG' 500U IM) is protective if given within 10 days of exposure to HBV; however, only use for persons with clear exposure to HBsAg-contaminated material (needle-stick or sexual contacts who are HBsAb-negative). Follow up for at least 6 months. See Table 3.4 for a summary of the investigation results in different HBV states.

Box 3.12 Guidelines on management of hepatitis A

Management of index case:*

- Exclude from work, school, or nursery until 7 days post-onset of jaundice.
- Advise on good hygiene practices, and identify possible source of infection.

House or sexual contacts within 14 days of exposure to index case:

- If aged 1–59: offer HAV vaccination.
- If aged ≥ 60 or chronic liver disease or chronic HBV or HCV: offer HAV vaccine and normal human Ig.

House or sexual contacts within >14 days of exposure to index case, or age <1 years old, please see guidance on HAV (2017) from Public Health England.⁵

* Source: data from Public Health England: Public health control and management of hepatitis A: 2017 Guidelines (<https://www.gov.uk/government/publications/hepatitis-a-infection-prevention-and-control-guidance>).

Table 3.4 Summary of HBV investigations

State	HBsAg	Anti-HBs	Anti-HBc IgM	Anti-HBc IgG	HBeAg	Anti-HBe	HBV DNA
Acute infection/ reactivation	+	–	+	–	+	–	+
Previous infection (immune)	–	+	–	+	–	+/ –	–
Vaccination (immune)	–	+	–	–	–	–	–
‘Inactive carrier’	+	–	–	+	–	+	$<10^5$
HBeAg +ve CHB	+	–	–	+	+	–	$>10^5$
HBeAg –ve CHB	+	–	–	+	–	+	$<10^5$

CHB, chronic hepatitis B.

Hepatitis C

HCV RNA is usually detectable in serum by PCR within 8 weeks following exposure, but may be earlier. Transmission is predominantly through blood exposure. Sexual or perinatal transmission are rare (<5% risk). Acute hepatitis C accounts for <5% of cases of acute viral hepatitis in the United Kingdom (UK). Most cases are asymptomatic; <25% develop an increase in serum bilirubin, and serum ALT is usually <1000U/L. The presence of HCV RNA in serum is the first evidence of HCV infection and is detectable within 2 months following exposure. Anti-HCV enzyme-linked immunosorbent assay (ELISA) tests become positive between 2 and 6 months after exposure.

The primary goal of HCV therapy is to cure the infection with the new direct acting antivirals (DAAs). Cure is defined as achieving a sustained virological response (SVR) defined as undetectable HCV RNA. The aims are to: (1) prevent the complications of HCV-related liver and extrahepatic diseases; (2) improve quality of life and remove stigma; and (3) prevent onward transmission of HCV.

All patients with HCV, regardless of previous therapy, should be considered for treatment. Overall, cure rates of 95% or above, approaching 100%, can be achieved with the new HCV DAAs.

References

5. Public Health England (2017). *Public health control and management of hepatitis A: 2017 guidelines*.  <https://www.gov.uk/government/publications/hepatitis-a-infection-prevention-and-control-guidance>.

Alcoholic hepatitis

- Acute hepatitis may be asymptomatic or present with nausea, vomiting, and anorexia, rarely RUQ pain. Fever may reflect severe liver damage, but infection needs to be excluded. Most patients who present with alcoholic hepatitis have cirrhosis at presentation.
- The term alcoholic hepatitis is a misnomer, as the transaminases rarely exceed 200U/L and are always <400U/L. AST is always higher than ALT (this is in contrast to most other liver diseases).
- Investigations are summarized in Table 3.5.

Practice points

- AST level is normally > ALT level, and both are usually <200U/L in alcoholic hepatitis. Never diagnose alcoholic hepatitis if AST or ALT exceed 400U/L.
- Muscle injury or excessive exercise can increase both AST and ALT.
- Very high AST or ALT levels (i.e. >1000U/L) should suggest paracetamol (acetaminophen) overdose, ischaemia, viral hepatitis, or autoimmune hepatitis. In paracetamol overdose, AST or ALT can be >10 000 U/L.

Management

- Admit most patients to hospital, unless mild (bilirubin <50 micromol/L, normal PT) or patient in abstinent environment.
- Give thiamine (100–200mg/day), folic acid, and multivitamins.
- Prescribe detox regime (e.g. reducing dose of chlordiazepoxide). Review the patient, as the dose $\pm$ frequency may need to be increased.
- Monitor and correct K^+ , Mg^{2+} , PO_4^{3-} , and glucose.
- Start a high-calorie, high-protein (1.5g/kg of body weight) diet. Low-protein diets are contraindicated.
- If clinically suspected, start broad-spectrum antibiotics (e.g. cefotaxime $\pm$ fluconazole (50–100mg IV daily) as prophylaxis against fungal infections.
- Patients with a Glasgow Alcoholic Hepatitis score (GAHs) (see Table 3.6) of ≥ 9 or discriminant function score (see Box 3.13) of ≥ 32 are classed as having severe alcoholic hepatitis and should be treated with prednisolone 40mg/day for 4 weeks. The only practical contraindication is untreated sepsis. If there is doubt, then give broad-spectrum antibiotics for 24–48h prior to steroids. An alternative to treatment with steroids is pentoxifylline (400mg tds PO)—a large multicentre trial STOPAH will shortly publish the results comparing steroid versus pentoxifylline therapy in this group.
- Delirium tremens or severe agitation may be managed with low-dose diazepam or oral clomethiazole PO (➡ Acute alcohol withdrawal, pp. 436–7; ➡ Acute alcohol withdrawal, p. 718–19). Treat seizures in the standard way (➡ Status epilepticus (tonic-clonic), p. 408–9; ➡ Acute alcohol withdrawal, p. 436–7).

Table 3.5 Investigations for alcoholic hepatitis

U&Es and LFTs	↑ bilirubin may be up to 800 micromol/L; albumin is often reduced; renal failure (including HRS) may occur in severe alcoholic hepatitis
PT	↑ PT usually signifies underlying cirrhosis
FBC	↑ WBC with left shift may occur (even without proven infection); ↓ Hb and ↓ platelets suggest splenomegaly secondary to cirrhosis
Septic Screen	Screen for bacterial or fungal infections—blood, urine, and ascitic fluid (send for microscopy and culture for all samples). Screen for HBV, HCV, and HIV, if not already performed
US	To exclude other causes of jaundice

Table 3.6 Calculation of Glasgow Alcoholic Hepatitis score (GAHs)*

Score given	1	2	3
Age	<50	≥50	—
WCC ($\times 10^9/L$)	<15	≥15	—
Urea (mmol/L)	<5	≥5	—
INR	<1.5	1.5–2.0	≥2.0
Bilirubin (micromol/L)	<125	125–250	>250

Score >9 = 50% mortality at 28 days if untreated (20% if treated with steroids).

* Reproduced from Gut, 'Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score', Forrest EH, et al. 54(8), pp. 1174–9, copyright 2005, with permission from BMJ Publishing Group Ltd.

Box 3.13 Calculation of Discriminant Index (DF)

$$DF = \frac{(\text{bilirubin})}{17} + (\text{prolongation of PT} \times 4.6)$$

For example: serum bilirubin of 340 micromol/L and PT of 17s (control 12s) would score = $(340/17) + [(17 - 12) \times 4.6]$, i.e. $20 + 23 = 43$.

- Mortality is 32% if $DF \geq 32$ if not treated with steroids.

Drug-induced hepatitis

Patients with drug-induced jaundice should be monitored three times per week or admitted for observation, as many are serious and may not resolve. Stop the suspected drug immediately, and observe. Look for rash and eosinophilia, and exclude other causes (see Box 3.14). This is important, as drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, potentially life-threatening drug-induced hypersensitivity reaction that includes skin eruption, haematologic abnormalities (eosinophilia, atypical lymphocytosis), lymphadenopathy, and internal organ involvement (liver, kidney, lung). (For paracetamol overdose, see ➡ Acute liver failure: assessment and investigations, pp. 276–7.) Drugs causing jaundice are listed in Box 3.14. Drugs causing a rise in transaminases, but rarely causing jaundice, are not listed. All drug-induced causes of jaundice should be reported to the Medicines and Healthcare Products Regulatory Agency, as drug-induced jaundice is associated with poor prognosis (yellow pages at the back of the BNF).

Box 3.14 Common drugs that cause jaundice

Hepatic

- Paracetamol.
- Rifampicin.
- Allopurinol.
- NSAIDs.
- Halothane.
- Methyldopa.
- Hydralazine.
- Isoniazid.
- Phenytoin.

Cholestatic

- Chlorpromazine.
- Flucloxacillin.
- Azathioprine.
- Captopril.
- Co-amoxiclav.
- Penicillamine.
- Erythromycin.
- Anabolic steroids.
- Oral contraceptive.

Mixed

- Sulfonamides.
- Sulfasalazine.
- Carbamazepine.
- Dapsone.
- Ranitidine.
- Amitriptyline.
- Nitrofurantoin.
- Co-amoxiclav.

Autoimmune hepatitis

This is characterized by elevated transaminases, up to a few thousand, usually <2000U/L, positive anti-smooth muscle (SM) antibodies, $\pm$ anti-liver kidney-1 (LK-1) antibodies, positive ANA, and raised IgG (polyclonal). Total globulins (total protein–albumin) should be <35g/L in health. $\uparrow$ globulin (>45g/L) should always raise suspicion of autoimmune hepatitis. Confirm with liver biopsy. Treatment: steroids (prednisolone 30–40mg od) $\pm$ azathioprine (1mg/kg) as a steroid-sparing agent once excluded viral hepatitis (i.e. HBsAg negative). If there is failure to respond in a young patient (<30 years), consider Wilson's disease.

Acholuric jaundice

This is characterized by absence of bilirubin in the urine. May be caused by haemolytic anaemia (previous history, excess urinary urobilinogen, splenomegaly, reticulocytosis, etc.) or a congenital disorder of conjugation (Gilbert's syndrome, 2% of the population). Fasting (<400cal) for 48–72h will increase serum unconjugated bilirubin in patients with Gilbert's syndrome (bilirubin rarely >80 micromol/L).

Sepsis

Any severe infections may cause jaundice (including pneumonia). Most severe with intra-abdominal sepsis. LFTs may be cholestatic or characterized by a predominant rise in bilirubin levels only. Exclude other causes, and treat infection with antibiotics $\pm$ surgical drainage.

Ischaemic hepatitis

Presentation

Occurs with significant hypotension or hepatic arterial occlusion. Predisposing factors include CCF $\pm$ hypoxia. In its mildest form, it manifests as mildly deranged LFTs (hepatitic picture, $\uparrow$ PT) in a patient with CCF, and in its most severe form, it may present as acute liver failure. Look for hypoxia, hypotension (may have normalized by the time of assessment—look at anaesthetic charts), signs of arteriopathy (abdominal bruits from hepatic arterial occlusion), signs of RVF on the ECG (AF is a rare cause). May cause confusion $\pm$ encephalopathy. Exclude other causes of hepatitis (➡ Jaundice: assessment, pp. 260–1).

Management

Most will respond to correction of the underlying aetiology. Correct hypotension (➡ Shock: assessment, pp. 330–1), and give O_2 to correct hypoxia. If the hepatic artery or coeliac axis is occluded, prognosis is poor and depends on the extent of hepatic necrosis. Usually age and the extent of disease preclude salvage surgery. Discuss with a specialist centre. If signs of severe (acute) liver failure are present, see ➡ Acute liver failure: management, pp. 278–9 for guidance. Most patients are not fit enough for liver transplantation.

Obstructive jaundice

See ➞ Biliary obstruction, pp. 272–3.

Gallstone disease

Gallstone disease affects 10–20% of the population. The stones may be predominantly cholesterol (>80%), pigment stones (<25% of cholesterol; multiple, irregular, friable), or mixed (faceted, calcium-containing). The majority are asymptomatic and diagnosed incidentally. Some risk factors include ♀ sex, age (over 40), pregnancy, obesity, and rapid weight loss.

Complications of gallstones

- Biliary colic.
- Obstructive jaundice.
- Cholecystitis ± empyema and gangrene of gall bladder.
- Cholangitis septicaemia or liver abscesses.
- Acute pancreatitis (➞ Acute pancreatitis: assessment, pp. 284–5).
- Perforation and peritonitis.
- Gall bladder fistula, gallstone ileus.

Biliary colic

Presentation

Abdominal pain (RUQ) radiating to the epigastrium, back, or shoulders, associated with nausea and vomiting. Attacks commonly follow a heavy meal and pass spontaneously. Differential diagnosis includes acute MI, leaking aortic aneurysm, peptic ulcer, intestinal obstruction or ischaemia, pancreatitis, renal colic, and pneumonia.

Investigations

USS to detect the stone and gall bladder distension. Urine microscopy, CXR, and ECG will help exclude other conditions.

Management

- Pain relief: can usually be achieved with NSAIDs (first line) ± opioids.
- Laparoscopic cholecystectomy in the longer term. If the patient is not a surgical candidate, medical dissolution of gallstones can be attempted with ursodeoxycholic acid (UDCA) (10–14mg/kg daily, at bedtime).

Acute cholecystitis

Presentation

Sudden-onset severe RUQ pain and symptoms, similar to biliary colic, with fever and persisting symptoms. Persistent vomiting suggests a bile duct stone. Physical signs include fever, tachycardia, sweating, RUQ tenderness, and peritonism, especially in inspiration (Murphy's sign), $\pm$ palpable gall bladder (rare). Jaundice (~33%) suggests obstruction of the common bile duct (CBD). Acalculous cholecystitis is seen in the elderly or patients with coexisting disease or trauma, in the ITU, and in those on TPN. Mortality may be high.

Investigations

- *Blood tests* $\uparrow$ WCC is usual. LFTs may show $\uparrow$ bilirubin, and cholestatic LFTs; $\pm$ $\uparrow$ amylase.
- *USS* Should demonstrate gallstones or biliary sludge $\pm$ thickening of gall bladder wall $\pm$ peri-cholecystic fluid.
- *AXR* Gallstones visible in ~10% of patients. Local peritonitis may produce a 'sentinel loop'.
- *Hepatobiliary iminodiacetic acid (HIDA) scan* Using ^{99}Tc -label is usually diagnostic.

Management

- NBM and IV fluids; insert an NG tube if there is severe vomiting.
- Antibiotics should cover enteric organisms and *Enterococcus* (e.g. cefuroxime 750mg IV tds + metronidazole 500mg IV tds).
- Early inpatient laparoscopic cholecystectomy is the treatment of choice.
- Complications include perforation, gallstone ileus, or fistula.

Biliary obstruction

Biliary obstruction or apparent biliary obstruction will be associated with either a dilated or a non-dilated biliary system, and the patient may be either septic or aseptically. Biliary dilatation in patients with mechanical biliary obstruction may not always be apparent on USS. See Box 3.15 for causes of biliary obstruction.

Presentation

- Jaundice $\pm$ fluctuation.
- RUQ pain $\pm$ tenderness (may be painless).
- Fever (indicates infection or cholecystitis).
- Itching.
- Dark urine $\pm$ pale stools (not very useful in practice).
- Septic shock.

Investigations

- *Blood tests* $\uparrow$ WCC indicates sepsis. U&Es may indicate renal failure or pre-renal uraemia. LFTs show $\uparrow$ bilirubin, $\uparrow\uparrow$ ALP, and $\uparrow\uparrow$ GGT; $\uparrow$ amylase with concomitant pancreatitis; transient $\uparrow$ ALT, AST with passage of a stone and persistent in cholangitis (usually $\uparrow \leq 400$ U/L; higher suggests hepatitis). Blood cultures and CRP mandatory.
- *USS* This is mandatory and should be performed within 12h, if possible, to demonstrate the presence of dilated ducts $\pm$ gallstones. Post-cholecystectomy slight dilatation (~ 0.8 cm) of CBD is normal.
- *AXR* Aerobilia may indicate a gas-forming organism or recent instrumentation. There may be localized ileus.
- *ERCP* Shows stones in CBD and allows examination of GIT and ampulla to exclude other pathology. Give broad-spectrum antibiotics if intervention is planned.
- *MRCP* Magnetic resonance cholangiopancreatography is a very accurate non-invasive investigation.
- *CT* Useful, especially if malignancy suspected. Perform full-staging CT if malignancy present.

Poor prognostic features (depend on the cause)

- Elderly (>65 years).
- Shock.
- Renal failure.
- Cholangitis with cirrhosis, liver abscess, or high malignant stricture.
- Cholangitis following transhepatic percutaneous cholangiography.
- Acute pancreatitis.

Management

(See Fig. 3.1.)

- Analgesia, NBM, IV fluids.
- Antibiotics (e.g. cefotaxime or ciprofloxacin + amoxicillin) if septic.

- Emergency decompression of the biliary system by:
 - ERCP.
 - Percutaneous drainage.
 - Surgical decompression.
- Follow-up with LFTs, CRP, and temperature.
- Repeat MRCP $\pm$ ERCP when well if there is concern regarding missed stones or further anatomic abnormality.
- Repeat USS or CT liver scan to look for hepatic abscesses.

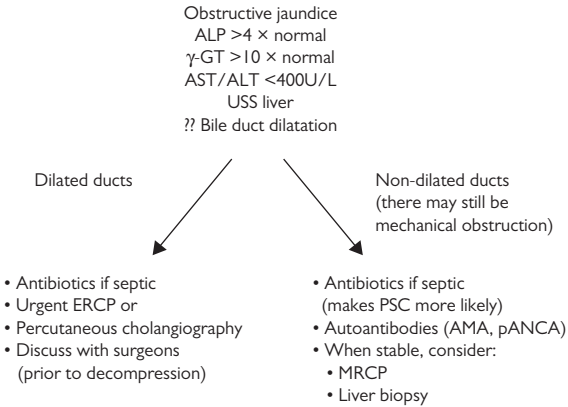


Fig. 3.1 Management algorithm for biliary obstruction. NB In cirrhosis, there may be no duct dilatation with biliary obstruction.

Box 3.15 Causes of biliary obstruction

Mechanical obstruction

- Gallstones.
- Malignancy (pancreatic carcinoma, nodes, secondary deposits, cholangiocarcinoma).
- Post-operative stricture.
- Cavernous transformation of portal vein.
- Parasitic infection (e.g. *Ascaris*).

Intrahepatic cholestasis

- PSC.
- PBC.
- Cholestatic drug reaction.

Ascites

Presentation

The patient may present with symptoms due to the fluid (abdominal distension, weight gain, abdominal pain), the underlying cause (jaundice, haematemesis, fever or night sweats, frothy urine due to proteinuria), or complications of ascites (dyspnoea, anorexia, reflux oesophagitis, herniae, pleural effusions, scrotal or leg oedema, peritonitis). Ask specifically about alcohol, risk factors for chronic liver disease, GI bleeding (portal hypertension), previous pancreatitis, risk factors for TB, cardiac history, exercise tolerance, and menstrual history (? ovarian malignancy) (see Box 3.16).

Differential diagnosis

- Ovarian cyst.
- Obesity (simple or metabolic).
- Pregnancy.
- Abdominal mass.

Investigations

- *Blood tests* U&Es, glucose, FBC, PT, LFTs, blood cultures, amylase.
- *Ascitic tap* An ascitic tap should be carried out in all patients, unless a diagnosis of malignant ascites is certain. Inoculate blood culture bottles, and send the fluid in a sterile pot for microscopy and WBC (➡ Ascitic tap (paracentesis), p. 841).
- *Imaging* Plain AXR shows a ground-glass pattern, with loss of the psoas shadow. USS can detect as little as 30mL. Note the size and texture of the liver and spleen; check the patency of hepatic veins (ask for Doppler US). CT scan may be required.
- *Urine* Urine Na⁺ (cirrhotic ascites), 24-h protein.

Management

Patients with symptomatic ascites may need admission. Treat the underlying cause.

- *Cirrhotic ascites:* salt-restrict to 80–120mmol/day (corresponding to 4.6–6.9g salt/day). This includes avoiding normal saline infusion, if possible.
- *Paracentesis:* if tense or moderate ascites, drain all ascites as quickly as possible (maximum 25L in 5h), and simultaneously give 8g of albumin per litre of ascites removed as 20% albumin (not required for malignant or exudative ascites). Do not paracentese if the patient has spontaneous bacterial peritonitis (SBP), as this can precipitate HRS.
- *Diuresis:* be cautious if starting diuretics in renal failure, hyponatraemia or abnormal serum K⁺ concentration. Start spironolactone at 100mg/day, increasing to 400mg/day (100mg per week). Add furosemide 40mg/day if response is poor. Stop all diuretics if severe hyponatremia (<120mmol/L), progressive renal failure, worsening hepatic encephalopathy, or incapacitating muscle cramps. Do not commence diuretics in patients who are hypovolaemic.
- If there is renal impairment (creatinine >140 micromol/L), consider giving an extra colloid and crystalloid volume challenge (e.g. 500mL of Gelofusine® over 1h, followed by 1L of normal saline over 4h).

- **Malignant ascites:** treatment is palliative and may include total paracentesis (including long-term tunnel lines) to make the patient more comfortable. Specialist advice should be sought for future management of the malignancy. There is no evidence to support giving albumin when draining non-cirrhotic malignant ascites.
- **Pancreatic ascites:** usually associated with a pancreatic pseudocyst and should be managed in consultation with surgical colleagues. ↑ amylase in ascitic fluid. If there is persistent pleural effusion, test for amylase in the pleural fluid, as there may be a pancreas–pleural fistula.
- **SBP:** occurs in up to ~15% of patients admitted with cirrhotic ascites and is frequently asymptomatic. The risk is ↑ with low ascitic protein (<15g/L). SBP is rare in non-cirrhotic ascites.
- **Diagnosis:** ascitic WCC >250 polymorphonuclear neutrophils (PMNs)/mm³. It is important to inoculate ascitic fluid into blood culture bottles at the bedside. If culture +ve but ascitic WBC low (known as bacterascites), repeat tap for microscopy and treat if WBC >250 PMNs/mm³.
- **Treatment:** broad-spectrum antibiotic for enteric organisms and Gram +ve cocci (e.g. cefotaxime). If bacterascites *and* systemic signs of infection, treat with antibiotics. Consider microbiology advice in patients on prophylactic antibiotics for SPB. Suspect TB ascites if there is predominant lymphocytosis. In patients with SBP, administration of IV albumin (1.5g/kg) at the time of diagnosis of infection and a second dose of 1.0g/kg on day 3 of antibiotic therapy may reduce the incidence of renal impairment and mortality.

Box 3.16 Causes of ascites

- Cirrhosis and portal hypertension.
- Malignant ascites.
- CCF.
- Pancreatic ascites.
- Hepatic venous obstruction.
- Nephrotic syndrome.
- Hypothyroidism.
- Infection (e.g. TB).

NB Ascites does not occur with portal vein thrombosis, congenital hepatic fibrosis, or other causes of non-cirrhotic portal hypertension, except during a major insult such as GI bleeding.

Practice points

- Salt-restrict to 4.6–6.9g/day—equivalent to a no added-salt diet, with avoidance of pre-prepared meals.
- Do not perform large-volume paracentesis until SBP is treated—can remove small volumes to aid breathing if ascites is very tense.
- No need to give albumin if draining malignant (exudative) ascites in non-cirrhotic patients.
- Stop all diuretics in severe hyponatraemia (Na^+ <120mmol/L).
- Stop furosemide in severe hypokalaemia (K^+ <3.0mmol/L).
- Stop aldosterone antagonists in severe hyperkalaemia (K^+ >6.0mmol/L).
- Maximum weight loss with diuresis should be 0.5kg/day in patients without oedema, and 1kg/day in patients with oedema.
- Diuretics should be discontinued permanently in patients with diuretic-induced complications.
- ACEIs are contraindicated in patients with cirrhosis due to the effect on renal function.

Acute liver failure: assessment and investigations

Acute liver failure (fulminant hepatic failure) is defined as a potentially reversible severe liver injury, with an onset of hepatic encephalopathy within 8 weeks of the appearance of the first symptoms and in the absence of pre-existing liver disease. A more recent classification is: hyperacute liver failure—encephalopathy within 7 days of jaundice; acute liver failure—encephalopathy within 8–28 days of jaundice; subacute liver failure—encephalopathy within 29–84 days of jaundice.

Presentation

- The history may point to a cause (see Box 3.17). Ask about recent viral illnesses, paracetamol, alcohol, and drug history (including herbal, OTC, and recreational drugs, and anabolic steroids). Signs of chronic liver disease, including splenomegaly, are typically not present (unless ‘acute-on-chronic’). If present, consider an acute presentation of Wilson’s disease, autoimmune chronic active hepatitis, or lymphoma. Frequently, the presenting feature is a complication of liver failure. Patients with paracetamol overdose (OD) may present with severe abdominal pain and retching.
- *Encephalopathy*: present in all cases (by definition) and conventionally divided into four grades (see Box 3.18). Cerebral oedema is heralded by spikes of hypertension and dysconjugate eye movements; papilloedema is rare. Unless treated, this progresses to decerebrate posturing (back, arms, and legs rigid; hands in flexion; opisthotonus) and brainstem coning. Refer to a specialist liver centre.
- *Metabolic disturbances*: hypoglycaemia and hyponatraemia are common. Other abnormalities include $\downarrow K^+$, respiratory alkalosis, and severe hypophosphataemia. Lactic acidosis carries a poor prognosis.
- *Cardiovascular abnormalities*: spikes of systolic hypertension may reflect cerebral oedema. DBP falls as disease progresses with a vasodilated hyperdynamic circulation ($\downarrow$ SVR, $\uparrow$ cardiac output).
- *Respiratory failure*: hypoxia is relatively common and may be worsened by localized infection, aspiration, or atelectasis. Non-cardiogenic pulmonary oedema is seen in ~10%.
- *Renal failure*: indicates a worse prognosis with conservative treatment and may be due to HRS (☞ Hepatorenal syndrome, pp. 308–9) or acute tubular necrosis (ATN) (paracetamol).
- *Bleeding problems*: PT is prolonged and reflects the progression of the disease. Low-grade DIC may occur with bleeding from the GIT from gastritis or elsewhere. Subconjunctival haematoma is common in paracetamol-induced liver failure.
- *Infections*: bacterial and fungal infections [septicaemia, pneumonia, peritonitis, urinary tract infections (UTIs)] are more frequent due to impaired neutrophil function.

Investigations

- *Blood tests (daily)*: U&Es, glucose (and 2-hourly blood glucose testing), FBC, PT, LFTs (albumin is usually normal on admission, unless 'acute-on-chronic'), PO_4^{3-} , ABGs. Blood group and cross-match on admission.
- *Blood tests (for diagnosis)*: viral serology (HAV IgM, HBsAg, HBc Ab IgM, delta in HBsAg +ve, EBV, CMV, HSV), drug screen (especially paracetamol—but may be normal by the time of presentation), plasma caeruloplasmin (if <50 years $\pm$ 24-h urine copper).
- *Bacteriology*: blood cultures, urine, sputum $\pm$ ascites (if present) MC&S daily (including fungal cultures). Throat and vaginal swabs.
- *USS (liver)*: to assess hepatic veins, portal vein patency, size (if possible), spleen size, and nodes (lymphoma).
- *ECG/CXR*: repeat CXR daily (infection/ARDS).
- *Electroencephalogram (EEG)*: may be helpful in the assessment of hepatic encephalopathy, though not widely used.
- *Liver biopsy*: rarely necessary but will exclude underlying malignant infiltration or cirrhosis where the diagnosis is in doubt. The transjugular approach is preferred, as it carries a lower risk of haemorrhage (➡ Percutaneous liver biopsy, p. 845).

Box 3.17 Causes of acute liver failure in the UK

- Drug-induced hepatitis (58%) (➡ Drug-induced hepatitis, p. 268): paracetamol OD (➡ Paracetamol: assessment, p. 772). Less commonly, halothane, isoniazid, sulfonamides, NSAIDs, phenytoin, valproate, penicillins, MAOIs, ecstasy, sulfasalazine, disulfiram, and ketoconazole.
- Viral hepatitis (36%) (➡ Viral hepatitis, p. 262–4): hepatitis A, B, delta co-infection in HBsAg +ve carrier, non-A/non-B (nAnB) (not HCV in the UK), E; less commonly CMV, EBV, and HSV.
- Toxins: *Amanita phalloides* (these mushrooms are available in the UK), herbal remedies, carbon tetrachloride (CCl_4).
- Malignancy: lymphoma, malignant infiltration.
- Vascular: Budd–Chiari syndrome, veno-occlusive disease, ischaemic injury (shock and hypotension).
- Miscellaneous: Wilson's disease (not strictly acute, as many are cirrhotic, but in all clinical respects similar), autoimmune hepatitis, malignant hyperthermia (including ecstasy), fatty liver of pregnancy, PET/HELLP syndrome, Reye's syndrome.

Box 3.18 Grades of hepatic encephalopathy

- *Grade 1*: drowsy but coherent; mood change.
- *Grade 2*: drowsy, confused at times, inappropriate behaviour.
- *Grade 3*: very drowsy and stuporose but rousable; alternatively, restless, screaming.
- *Grade 4*: comatose, barely rousable.

Acute liver failure: management

The mainstay of treatment is support until the acute insult resolves. If a patient fulfils the criteria for liver transplantation (see Box 3.19) on or during their admission, they should be referred to a centre where liver transplantation is available.

It is vital to discuss all cases of severe liver injury with one of the regional liver transplant centres, even though the patients may not fulfil the criteria (see Box 3.20), as it generally takes up to 48h to obtain an emergency graft, and delay in referral can result in failure to procure an adequate graft. All of these centres are also experienced in managing this serious illness. None of the known causes of acute liver failure respond well to medical therapy. Steroids may be of benefit in patients with lymphoma or autoimmune hepatitis, but by the time most patients present, it is usually too late. All patients should be admitted to a HDU or ITU.

- **Paracetamol OD:** give acetylcysteine (➡ Paracetamol: assessment, p. 772). The benefit of acetylcysteine may be evident up to 48h, and possibly longer.
- **General measures:** nurse supine (not 45°, as often stated). Keep in a peaceful environment. Insert an arterial line and a CVP line for monitoring and, if possible, a PA catheter (Swan–Ganz) to optimize the haemodynamic status.
- **Coagulopathy:** PT is the best indicator of liver function. Avoid giving FFP, unless there is bleeding or undergoing surgical procedures or line insertion. Factor concentrates may precipitate DIC. PT may rise and fall precipitously and should be measured twice daily if deteriorating. Give vitamin K 10mg once only IV. Give platelet support if thrombocytopenic and bleeding.
- **Encephalopathy:** see ➡ Hepatic encephalopathy, p. 281.
- **Cerebral oedema:** develops in 75–80% of patients with grade 4 encephalopathy. ICP monitoring is used in some centres. Avoid NG tube if not sedated and intubated. Give mannitol (0.5–1.0g/kg); if in renal failure, watch for fluid overload. Hyperventilation decreases the ICP at the expense of cerebral blood flow—only consider when herniation is imminent. Epoprostenol and acetylcysteine may decrease the ICP. Hypertension is almost always secondary to raised ICP and should be treated with mannitol, as already described; antihypertensive drugs may precipitate brainstem coning. There is no evidence that giving lactulose or neomycin affects prognosis or prevents grade 3–4 encephalopathy. Flumazenil is reported to improve encephalopathy but does not affect outcome. Seizures should be treated in the usual way (➡ Status epilepticus (tonic–clonic), pp. 408–9).
- **Haemodynamic support:** correct hypovolaemia with colloid or blood, but avoid fluid overload. Persistent hypotension may respond to NA infusion or glypressin.
- **Metabolic changes:** monitor glucose 2-hourly, and give 10% or 50% glucose to keep glucose >3.5mmol/L. Monitor serum PO_4^{3-} (often very low), replace with IV (9–18mmol/24h) if <0.4mmol/L. Nutrition: ileus is often present, but drip enteral feeding (10–20mL/h) is enteroprotective.
- **Renal failure** (➡ Hepatorenal syndrome, pp. 308–9): monitor renal function (renal failure occurs in ~70% cases). Treat by haemodiafiltration, rather than haemodialysis.

- *Respiratory support*: monitor O_2 saturations continuously, and give O_2 by mask if $SpO_2 < 90\%$. Ventilate when grade 3 or 4 coma [avoid ETT ties which compress the internal jugular veins (IJVs)].
- *Infection*: start prophylactic antibiotics and antifungals (e.g. cefotaxime and fluconazole).
- *Wilson's disease*: consider penicillamine and IV vitamin E.

Box 3.19 Indications for liver transplantation (King's College criteria)

- Paracetamol OD with arterial pH < 7.3 (admission).
- Grade 3 or 4 encephalopathy and PT $> 100s$.

Or in the absence of the above:

ALL three of the following or:

- PT $> 100s$.
- Creatinine > 300 micromol/L.
- Grade 3–4 encephalopathy.

Any three of the following:

- PT $> 50s$.
- Jaundice to encephalopathy > 7 days.
- Age < 10 years or > 40 years.
- Bilirubin > 300 micromol/L.
- Unfavourable aetiology (i.e. non-paracetamol, not hepatitis A, not hepatitis B).

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Box 3.20 Management key points: acute liver failure

- Discuss all cases with the regional liver transplant centre.
- Nurse supine and keep the patient in a peaceful environment.
- *Correct hypovolaemia* (colloid or blood) *and electrolyte disturbances* (e.g. hypokalaemia, hypophosphataemia). Avoid fluid overload. Persistent hypotension may respond to NA or vasopressin infusion.
- *Encephalopathy*: lactulose 10–15mL tds. Phosphate enemas.
- *Cerebral oedema*: if signs of cerebral oedema (e.g. hypertension) are present, give mannitol (100mL of 20% mannitol).
- *Coagulopathy*: monitor PT. Give vitamin K (10mg IV once only). Avoid FFP, unless bleeding or undergoing surgical procedures. Platelet support if thrombocytopenic and bleeding.
- *Hypoglycaemia*: monitor BM 2-hourly, and treat with 10% or 50% glucose to keep glucose > 3.5 mmol/L.
- *HRS*: terlipressin and IV albumin (☞ Hepatorenal syndrome, p. 308–9).
- *Sepsis*: prophylactic antibiotics/antifungals (e.g. cefotaxime and fluconazole).
- *Treat the underlying cause*: e.g. in paracetamol OD, give NAC; stop the suspected drug.
- *Monitor*: pulse rate, BP, O_2 saturations, CVP, urine output/fluid balance, grade of encephalopathy, and renal function closely in HDU or ITU.
- *Pain management*: paracetamol (2–4g/day in mild cirrhosis; avoid in severe cirrhosis or acute liver injury); avoid NSAIDs (risk of haemorrhage, renal failure, and diuretic-resistant ascites); opioids (use with caution; reduce dose).

'Acute-on-chronic' liver failure

Patients with chronic liver disease from cirrhosis may present with acute decompensation due to a variety of causes (see Box 3.21).

Clinical features

- Ask specifically for a history of previous hepatitis, jaundice, alcohol intake, previous drug history (including herbal and OTC). Weight loss may point to malignancy. Pruritus, pigmentation, and xanthelasma in a young woman may be due to PBC.
- Examine for evidence of long-standing liver dysfunction: leuconychia, palmar erythema, clubbing, spider naevi, gynaecomastia, and small testes. Splenomegaly and distended abdominal veins signify portal hypertension.
- Examine specifically for features of decompensation: encephalopathy (confusion, 'liver flap'), ascites, oedema, jaundice, or fever.

Investigations

Unless the cause for decompensation and the diagnosis for the pre-existing liver disease are known, the patient warrants full investigation (➡ Jaundice: assessment, pp. 260–1).

Management

As for patients with acute liver failure, the mainstay of treatment is supportive. The decision on how aggressively you manage the patient (i.e. admission to ITU, invasive monitoring, etc.) depends on the previous diagnosis, on a reversible element to the acute insult, and whether the patient is a candidate for liver transplantation. They have less capacity to regenerate their hepatocytes, and the prognosis of patients requiring mechanical ventilation and haemodynamic support is very poor without a transplant.

Sepsis

Start 'blind' treatment if there is fever or ↑ WCC (e.g. cefotaxime), and be guided by culture results (e.g. a third-generation cephalosporin, bacterial peritonitis, ➡ Ascites, pp. 274–5). Add IV fluconazole as an antifungal agent.

Box 3.21 Causes of acute decompensation of chronic liver disease

- Intercurrent infection:
 - SBP.
 - Pneumonia.
 - Skin infections.
- Acute GI haemorrhage.
- TIPS.
- Additional hepatotoxic insult:
 - Alcoholic binge.
 - Acute viral hepatitis.
 - Hepatotoxic drugs.
- Drugs:
 - Sedatives/narcotics.
 - Diuretics.
- Metabolic derangement:
 - Hypoglycaemia.
 - Electrolyte disturbance.
- Major surgery.
- Constipation.
- Progression of disease.
- Development of hepatocellular carcinoma (HCC).

Hepatic encephalopathy

Hepatic encephalopathy is a neuropsychiatric disturbance of cognitive function in a patient with acute-on-chronic liver disease (➡ 'Acute-on-chronic' liver failure, p. 280).

Clinically, there is usually an altered conscious level, asterixis (liver flap), abnormal EEG, impaired psychometric tests, and an elevated serum ammonia concentration (useful in monitoring treatment, and not in diagnosis of hepatic encephalopathy). Patients may present with Parkinsonian features. However, in patients with chronic liver disease, it may be subclinical, with subtle changes in awareness or attention span. It is graded (see Box 3.18). Consider CT head, as intracranial bleed may present with a reduced conscious level.

Treatment

The aim of treatment is to improve morbidity.

- Exclude other causes of confusion (➡ Confusional states and delirium: assessment, p. 432).
- Identify and correct the precipitating causes (see Box 3.22).
- Give lactulose—this semi-synthetic disaccharide is poorly absorbed. It is digested in the large bowel and undergoes fermentation. This alters faecal pH and nitrogen utilization by bowel flora. Lactulose enemas can be given if the patient cannot take lactulose orally or via an NG tube.
- Lactitol has a similar action to lactulose but has fewer side effects. Titrate the dose to achieve 2–3 bowel motions per day.
- Phosphate enemas help to purge the large bowel. Most useful in the context of an acute food load (e.g. GI bleeding).
- Dietary restriction is controversial and may be harmful in malnourished patients. Ensure adequate calorie intake.

Box 3.22 Common precipitants of hepatic encephalopathy

- Infection (including SBP—may be asymptomatic).
- Hypovolaemia (including large-volume paracentesis).
- Electrolyte disturbance (e.g. hypokalaemia).
- Metabolic alkalosis.
- GI bleed.
- Constipation.
- Hypoxia.
- Hypoglycaemia.
- Drugs (e.g. sedatives, alcohol, or tranquillizers).
- HCC (rare).
- Hepatic or portal vein thrombosis.
- Portosystemic shunt (e.g. TIPS).

Liver abscesses

Presentation

- Commonly present with fever and night sweats, nausea, vomiting, weight loss, or RUQ or intercostal pain.
- The underlying cause (e.g. appendicitis) may be silent or barely noticed. Ask about recent abdominal pain, altered bowel habit, diarrhoea, biliary colic, blood PR, or IBD.
- Ask about travel history, occupation (farming is a risk factor for *Echinococcus*), or contact with infected persons (TB).
- Intrauterine devices are a risk factor for actinomycosis, which can present with liver abscesses.
- Examine for jaundice, hepatomegaly, pleural effusions (commonly right-sided), intercostal tenderness (characteristic of amoebic abscesses), abdominal masses (tumour or inflammatory mass), and lymphadenopathy. Perform a rectal and vaginal examination for pelvic tumour.
- Severe infection may be associated with septic shock (➡ Sepsis syndrome and septic shock, pp. 336–7).

Causes

- Pyogenic organisms (appendicitis, diverticulitis, carcinoma, biliary).
- Amoebic abscess (*E. histolytica*).
- Hydatid cyst (*Echinococcus granulosus*).
- TB (very rare).

Investigations

- **U&Es:** renal impairment with sepsis.
- **LFTs:** non-specific, tend to be cholestatic; may be normal with amoebic abscess, ↓ albumin.
- ↑ CRP, ↑ ESR.
- **PT:** may be prolonged with multiple abscesses.
- **FBC:** leucocytosis, eosinophilia, non-specific anaemia.
- **Microbiology:** blood and urine cultures, as well as culture and Gram-stain any materials obtained from USS or CT scan (if there is suspicion of hydatid disease, aspiration is contraindicated). Amoebic and hydatid serology must be sent. Stool may contain amoebic cysts or vegetative forms.
- **Radiology:**
 - CXR (looking for effusion or pulmonary TB).
 - USS of the liver, biliary tree, and abdomen (iliac fossae, in particular) and CT scan with contrast, looking for masses. Both pyogenic and amoebic abscesses tend to be thick-walled; hydatid cysts are thin-walled, and there may be daughter cysts. Solid tumours are echodense but may have necrotic hypodense centres
 - Positron emission tomography (PET) scan will show up pyogenic foci in the liver and elsewhere (e.g. terminal ileitis); amoebic abscesses do not take up the label.

Management

- *Pyogenic abscess*: aspirate any large abscesses under US or CT guidance. Surgical or ERCP drainage are also potential options, depending on the position of the cyst(s). It is pointless to try and drain multiple abscesses. If there is a continuing intra-abdominal source, it is virtually impossible to eradicate liver abscesses without removing or dealing with that source (e.g. appendix). Broad-spectrum antibiotics (e.g. cefotaxime and metronidazole).
- *Amoebic abscess* (➡ Amoebic dysentery, p. 253): percutaneous aspiration—if cyst is at risk of rupture or if there is clinical deterioration or lack of response to treatment. Treat with metronidazole (or tinidazole), followed by diloxanide furoate. Secondary bacterial infection occurs in up to 20%.
- *Hydatid disease*: laparoscopic (or open) surgical de-roofing of the cyst is the treatment of choice. Albendazole may help reduce the risk of recurrence post-surgery or be used in inoperable cases. Percutaneous treatment via puncture, aspiration, injection, and re-aspiration (PAIR) is an acceptable alternative approach. Percutaneous aspiration alone is ineffective and should be avoided.
- *TB abscess*: anti-tuberculous therapy.

Practice points

- Pyogenic and amoebic abscesses cannot be distinguished on the basis of radiologic appearances alone.
- Ensure the source of the liver abscess is treated (e.g. appendix, biliary sepsis).

Acute pancreatitis: assessment

Acute pancreatitis is increasingly managed by physicians, particularly if it presents in an unusual way (e.g. chest pain).

Presentation

- Abdominal pain: epigastric or generalized, of rapid onset, but may occur anywhere (including chest); dull, constant, and boring. Radiation to the back or between the scapulae, often relieved by leaning forward (differential diagnosis is leaking aortic aneurysm).
- Nausea, vomiting, and dehydration $\pm$ jaundice.
- Peritonitis with epigastric tenderness, localized rebound tenderness, or generalized abdominal rigidity. An abdominal mass may indicate a pancreatic pseudocyst or an abscess. Bowel sounds usually absent.
- Tachycardia and hypotension; shock/collapse and respiratory failure in severe cases (especially in the elderly).
- Very rarely, signs of bleeding in the pancreatic bed, Grey–Turner's sign (ecchymosis in the flanks) or Cullen's sign (periumbilical bruising), tender red skin nodules (due to subcutaneous fat necrosis).
- Hypocalcaemic tetany.

Investigations

- *Amylase* Elevated, but not specific (see Box 3.23), especially if only up to 4 $\times$ upper limit of normal. A persistently raised amylase (several days to weeks) may indicate the development of a pseudocyst.
- *FBC* Raised haematocrit and leucocytosis.
- *U&Es* Urea may be raised with hypovolaemia.
- *Glucose* May be raised.
- *LFTs* AST and bilirubin often elevated, especially in gallstone pancreatitis. Disproportionately elevated GGT may indicate an alcohol aetiology.
- *Ca²⁺* Hypocalcaemia (unless precipitant was $\uparrow$ Ca²⁺).
- *CRP* Elevated: used to monitor progression of the attack.
- *ABGs* Mandatory; hypoxia $\pm$ metabolic acidosis.
- *AXR* Generalized ileus or sentinel loops (dilated gas-filled loops in the region of the pancreas). Look for evidence of pancreatic calcification (chronic pancreatitis) or biliary stone.
- *CXR* May show pleural effusion, elevated diaphragm, or pulmonary infiltrates.
- *USS* May confirm diagnosis of gallstones $\pm$ biliary obstruction, pseudocysts, and abscesses.
- *CT abdomen* Dynamic contrast-enhanced, is reliable at detection of pancreatic necrosis and grading severity, after 3–4 days.

Assessment of severity

- Severity of disease has no correlation with the elevation of serum amylase. Several prognostic indices have been published, but it takes 48h to fully appreciate disease severity (see Box 3.24).
- Mortality from acute pancreatitis is ~10% and rises to 40% in those developing a pancreatic abscess. Mortality is highest in those with a first episode of pancreatitis. Around 15% of patients presenting with acute pancreatitis have recurrent disease.
- No scoring system is perfect, and some take 48h to complete (e.g. Ranson, Glasgow).

Box 3.23 Causes of abdominal pain and elevated serum amylase

- Acute pancreatitis.
- Stomach or small bowel perforation.
- Perforated peptic ulcer.
- Mesenteric infarction.
- Acute liver failure.
- Acute cholecystitis or cholangitis.
- Renal failure (modest elevation).
- Diabetic ketoacidosis (DKA).

Box 3.24 Markers of severity in acute pancreatitis

At presentation

- Age >55 years.
- WBC $>16 \times 10^9/L$.
- Glucose $>10\text{mmol/L}$ (non-diabetic).
- LDH $>350\text{IU}$.
- AST $>250\text{IU/L}$.

During the first 48h

- Haematocrit fall $>10\%$.
- Urea rise $>10\text{mmol/L}$.
- Serum $\text{Ca}^{2+} <2.0\text{mmol/L}$.
- Base excess $>4\text{mmol/L}$.
- $P_a\text{O}_2 <8\text{kPa}$.
- Serum albumin $<32\text{g/L}$.
- Estimated fluid sequestration $>6\text{L}$.

Mortality: 0–2 criteria = 2%; 3–4 = 15%; 5–6 = 40%; >7 = 100%.

NB The presence of organ failure $\pm$ pancreatic necrosis defines severe acute pancreatitis.

Practice points

Severe acute abdominal pain is nearly always due to a surgical cause.

Acute pancreatitis: management

The principles of management are:

- Liaise with surgeons.
- Supportive measures: the majority will subside in 3–10 days.
- Careful observation for the development of complications.
- Identify the cause (see Box 3.25).

For key points in management, see Box 3.26.

Supportive treatment

- Establish IV access. If there is shock, markers of moderate to severe pancreatitis, hypoxia not readily correcting with O_2 , or other coexisting disease or in cases of elderly patients, insert a CVP line to help control fluid balance.
- Patients are usually severely volume-depleted—give prompt fluid replacement with crystalloids. Monitor urine output, and insert a urinary catheter if required.
- O_2 should be given if there is hypoxia on air (use continuous pulse oximetry in severe cases and 6-hourly for the first 48h for the rest, to monitor for respiratory failure).
- NBM initially. However, recent guidelines advocate a low-residue, low-fat, soft diet when the patient appears to be improving.⁶ The same guidelines advocate NG tube, over NJ (nasojejunal), feeding, mainly due to NJ placement being invasive and expensive.
- Monitor blood glucose regularly, and treat with insulin if high.
- Pain relief: NSAIDs $\pm$ opioids; pethidine causes the least spasm of the sphincter of Oddi.
- Antibiotic prophylaxis with cefuroxime decreases secondary infections.
- Octreotide (somatostatin analogue): this suppresses pancreatic enzyme secretion but is of unproven benefit.
- Peritoneal lavage: there is no proven benefit.
- H_2 -antagonists have not been shown to affect mortality.

Complications

(Seen in ~20% of cases.)

Local

- Abscess.
- Pseudocyst $\pm$ infection.
- Biliary obstruction.
- Ascites, pleural effusion.
- Fistula.
- Splenic, portal, or mesenteric.

Systemic

- Electrolyte imbalance.
- $\downarrow Ca^{2+}$, $\downarrow Mg^{2+}$.
- ARF.
- Shock.
- Respiratory failure.
- Sepsis vein obstruction.

Septic complications

Sepsis is the most common cause of death. This should be suspected when there is persistent fever, leucocytosis, pain/tenderness, or an overall clinical deterioration. These signs are an indication for multiple blood cultures and an abdominal CT. Pancreatic pseudocysts are more common in alcoholic pancreatitis (15% versus 3% in gallstone pancreatitis), but infection is more common in gallstone pancreatitis.

Biliary pancreatitis

Patients with acute pancreatitis and concurrent cholangitis need to undergo urgent ERCP within 24h.⁶ ERCP within 72h of presentation reduces complications and mortality in patients with severe gallstone pancreatitis. The benefit has not been demonstrated in mild cases. In the absence of cholangitis and/or jaundice, MRCP or endoscopic ultrasound scan (EUS) should be performed before ERCP if gallstones are suspected.

Indications for surgery

Infected pancreatic necrosis or pancreatic abscess. Radiologically guided percutaneous drainage is now preferred to surgery for pancreatic pseudocysts. Patients with mild pancreatitis, who have gallstones in their gall bladder, should be considered for cholecystectomy prior to discharge.⁶

Box 3.25 Causes of acute pancreatitis

Common (80%)

- Gallstones (including biliary microlithiasis or sludge) (60%).
- Alcohol (20%).

Rare (10%)

- Iatrogenic (ERCP or any form of abdominal surgery).
- Trauma (even seemingly minimal trauma, as pancreas is in a very vulnerable position, e.g. 'seat-belt sign' or bicycle handle-bar injury).
- Infections:
 - Viral: mumps, rubella, Coxsackie B, EBV, CMV, hepatitis A and B).
 - Bacterial: *Mycoplasma*.
 - Others: *Ascaris*, flukes (*Clonorchis sinensis*).
- Systemic vasculitis (SLE, PAN, etc.).
- Drugs (e.g. thiazides, furosemide, NSAIDs, sulfonamides, azathioprine, tetracyclines, and valproate; possibly steroids).
- Hypertriglyceridaemia (serum amylase falsely low).
- Hypercalcaemia or IV Ca^{2+} infusions.
- Hypothermia.
- Pancreatic carcinoma (3% present with acute pancreatitis).
- Miscellaneous: anatomical abnormalities (pancreas divisum, duodenal or periampullary diverticulae), scorpion bites, cystic fibrosis.

Unknown (10%)

Box 3.26 Management key points: acute pancreatitis

- Liaise with surgeons.
- Keep NBM.
- IV fluids.
- Analgesia (pethidine causes the least spasm of the sphincter of Oddi).
- Antibiotic prophylaxis (e.g. cefuroxime) decreases secondary infections.
- O₂ should be given if there is hypoxia on air.
- Gallstone pancreatitis: ERCP—within 72h of presentation in severe cases, within 24h if associated with biliary sepsis.
- Monitor urine output, O₂ sats, blood glucose, and CVP (if there is shock or markers of moderate to severe pancreatitis).
- Enteral nutrition (NG/NJ).
- Careful observation for the development of complications.

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Renal emergencies

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Acute kidney injury 1

Acute kidney injury (AKI), previously known as acute renal failure (ARF), is a common clinical presentation. AKI is present in 13–18% of patients admitted to hospital and in 30% of admissions to ITU. The inpatient mortality of AKI is 25–30%, although there are several variables affecting outcome to consider. In those patients with AKI requiring RRT, and with MOF, the mortality is as high as 80%. It is a clinical syndrome characterized by a rapid reduction in renal excretory function and glomerular filtration rate (GFR) over hours to weeks, leading to impaired control of extracellular volume, electrolytes, and acid–base balance. AKI is classically divided into pre-renal, renal (intrinsic), and post-renal. AKI has to be *distinguished from acute-on-chronic renal failure*. The latter is normally associated with anaemia, abnormal calcium phosphate, and small kidneys on USS $\pm$ history of pre-existing renal disease.

Definition

AKI is an abrupt (within 48h) reduction in kidney function, currently defined as an absolute increase in serum creatinine of $\geq 26\mu\text{mol/L}$, or a $>50\%$ increase in serum creatinine from baseline presumed to have occurred within 1 week, or a reduction in urine output (documented oliguria of $<0.5\text{mL/kg/h}$ for >6 consecutive hours). Serum creatinine and urine output are the best clinically available biomarkers for AKI used in common practice. Table 4.1 demonstrates the staging of AKI in adults [Kidney Disease Improving Global Outcomes (KDIGO)].

Table 4.1 Staging of AKI in adults (KDIGO)*

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR $\geq 0.3\text{mg/dL}$ ($\geq 26.5\mu\text{mol/L}$) increase	$<0.5\text{mL/kg/h}$ for 6–12h
2	2.0–2.9 times baseline	$<0.5\text{mL/kg/h}$ for $\geq 12\text{h}$
3	3.0 times baseline OR Increase in serum creatinine to $\geq 4.0\text{mg/dL}$ ($\geq 353.6\mu\text{mol/L}$) OR Initiation of RRT	$<0.3\text{mL/kg/h}$ for $\geq 24\text{h}$ OR Anuria for $\geq 12\text{h}$

* Reprinted from *Kidney International Supplements*, 2(1), ‘Section 2: AKI Definition’, 19–36, Copyright (2012), with permission from Elsevier.

Presentation

- May be asymptomatic.
- Elevated serum creatinine during biochemical screening.
- Detection of oliguria by nursing staff.
- Malaise, confusion, seizures, or coma.
- Nausea, anorexia, or vomiting.
- Oliguria or abnormal urine colour.

- Haematuria (pink, rather than frank, blood).
- Drug OD (e.g. paracetamol).
- Constitutional symptoms (arthralgia, rhinitis, respiratory).
- Sepsis.
- Vasculitic rash.
- MOF.

Diagnosing the cause of AKI

In the majority of cases, renal impairment can be resolved by adequate volume replacement, treatment of sepsis, and stopping nephrotoxic drugs. There are many causes of AKI. Acute tubular injury is the most common cause of intrinsic renal disease which is a consequence of pre-renal AKI. However, it is vital to identify the other potential causes of intrinsic renal disease as an underlying cause, as early specialist input is necessary for prompt diagnosis and treatment (see Box 4.1).

Box 4.1 Causes of AKI

Pre-renal

- Hypovolaemia.
- Shock.
- Hypotension (☞ Shock, p. 328–9):
 - Cardiac failure.
 - Sepsis.
- Renal artery emboli.
- Renal artery stenosis + ACEI.
- HRS.
- *Post-renal (obstructive)*
 - Renal vein thrombosis.
 - ↑ intra-abdominal pressure.
 - Intraluminal:
 - Stones.
 - Papillary necrosis.
 - Ureteric:
 - Stones.
 - Retroperitoneal fibrosis/tumour.
 - Bladder outlet obstruction:
 - Prostatic hypertrophy.
 - Neurogenic bladder.

Renal (parenchymal)

- Vasculitis [ANCA-associated vasculitis (AAV), cryoglobulinaemia, anti-GBM disease].
- Glomerulonephritis (SLE, AAV, IgA nephropathy).
- Acute tubular injury:
 - Ischaemia (e.g. hypotension).
 - Septicaemia.
 - Toxins [myoglobin, Bence Jones (BJ) proteins].
 - Drugs (e.g. gentamicin) or radiocontrast media.
 - Prolonged pre-renal oliguria.
 - Malaria.
- Thrombotic microangiopathy:
 - Accelerated hypertension.
 - HUS/thrombotic thrombocytopenic purpura (TTP)/DIC (☞ Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, p. 654).
- Scleroderma crisis.
- Interstitial nephritis:
 - Drugs (NSAIDs, antibiotics, PPIs).
 - Infections (*Streptococcus*, *Staphylococcus*, *Leptospirosis*, *Brucella*, Gram –ve sepsis, *Legionella*, HIV, hepatitis B and C).
- Calcium, urate, oxalate overload:
 - Tumour lysis syndrome (☞ Tumour lysis syndrome, p. 655).

Initial treatment includes:

- *Volume assessment* and fluid challenge (unless fluid-overloaded) to ensure adequate intravascular volume. Prescribe appropriate IV fluid, following the assessment of the patient's fluid status.
- *Review drug history*. Nephrotoxic drugs should be stopped, with dose reduction in other medications, according to renal function.
- *Care with opiates*, as these can accumulate with a reduced GFR.
- *Is the patient septic* (pyrexia, high CRP, leucocytosis)?
- *History*. Is there a history of hypertension, diabetes, prostatism, haematuria, or vascular disease?
- *Urgent USS* to look for obstruction, blood flow, size, cysts, and symmetry. NICE guidelines recommend USS within 6h if infected and obstructed kidneys are suspected; USS within 24h with no identified cause of AKI or at risk of obstruction.
- *Urinalysis and microscopy* to look for red or white cell casts, myoglobinuria, and haematuria.

Points to note in the history

- History of fluid loss [diarrhoea and vomiting (D&V), diuretics, bleeding, fever]. Diarrhoea may suggest hypovolaemia, or bloody diarrhoea may suggest HUS.
- History of sepsis (e.g. UTI, fever or hypothermia, bacterial endocarditis; symptoms may be non-specific in the elderly).
- Drug history: NSAIDs, ACEIs, angiotensin receptor blockers (ARBs), diuretics, antibiotics (in particular, aminoglycosides and amphotericin), drugs for HIV disease.
- Non-specific symptoms: myalgia, arthralgia, neurological signs, ophthalmic complications, sinusitis, haemoptysis, and skin rashes may suggest vasculitis.
- Past history of BP, DM, renovascular disease, liver disease, or cardiac failure.
- History or symptoms of urological obstruction.
- Patients with DM or myeloma have an ↑ risk of contrast-induced renal impairment (avoid volume depletion).
- Backache may suggest pelvi-ureteric obstruction. Consider aortic aneurysm or retroperitoneal fibrosis.
- Cholesterol emboli (aneurysms, absent pulses, rash, history of recent vascular intervention, e.g. angiography).
- Postpartum (HELLP syndrome, HUS, fatty liver, pre-eclampsia).
- Renal transplant patient.

The urine appearance may help (see Box 4.9).

Acute kidney injury 2

Assessment of severity

- *Fluid overload* (dyspnoeic with signs of pulmonary oedema, high JVP or CVP, peripheral oedema, gallop rhythm).
- *Hypovolaemia* or dehydration (postural hypotension, tissue turgor).
- *Hypotension* is a common cause of AKI and should be corrected.
- *Urine output*: anuria occurs in complete obstruction (usually low, e.g. prostate), rapidly progressive glomerulonephritis.
- *Hyperkalaemia* can be life-threatening. Look at ECG for signs, and measure serum K^+ .
- *Acidosis* causes hyperventilation and cardiac instability.

Risk factors for developing AKI include

- Age >75 years.
- Known chronic kidney disease.
- Cardiac failure.
- Peripheral vascular disease.
- DM.
- Sepsis.
- Liver disease.
- Nephrotoxic drugs.
- Use of iodinated contrast agents within the previous 1 week.

Poor prognostic features include

- Age >50 years.
- Infection (especially septicaemia).
- Burns (>70% of surface area).
- Rising urea (>16mmol/24h).
- Oliguria for >2 weeks.
- MOF (>3).
- Jaundice.

Main priorities

- Resuscitate and correct volume if depleted: early administration and aggressive fluid resuscitation.
- Remove nephrotoxic drugs or agents: review drug chart, and stop NSAIDs, ACEIs, ARBs, and diuretics if hypovolaemic. Stop metformin.
- Identify if the patient is septic, and treat with antibiotics.
- Exclude obstruction or major vascular injury.
- Identify the minority (~5%) that have intrinsic renal disease, since these are best managed by a specialist centre. These include:
 - Myeloma.
 - Glomerulonephritis.
 - Rhabdomyolysis (high CK).
 - Vasculitis.
 - Interstitial nephritis.

Assessment of patients with AKI

- Is there life-threatening hyperkalaemia, pulmonary oedema, or metabolic acidosis?
- What is the likely cause?
- Is the patient still passing urine?
- Does it look normal?
- RR and O₂ saturations.
- ECG.
- Urgent U&Es + ABGs.
- CXR.

Pre-renal (40–80%)

- Check postural BP and HR.
- Assess volume status.
- Sepsis screen.
- Drug review.

Renal (35–40%)

- Urinalysis and microscopy for blood/casts.
- Vasculitis, myeloma, and immunology screen.
- Drug history.
- Creatinine phosphokinase (CPK)/myoglobin in urine.

Post-renal (2–10%)

- May or may not have complete anuria.
- Upper tract urological obstruction needs referral to the urologist.
- Nephrostomy/stenting as soon as possible and within 12h of diagnosis.

Patients requiring RRT should be stabilized on a general ICU with haemofiltration and support, until safe to transfer care to a renal unit. It is particularly important to urgently transfer care for patients with intrinsic renal disease.

Acute kidney injury: investigations

Blood tests

- **U&Es** Urea is disproportionately raised in pre-renal failure, GI bleed, catabolic states, and corticosteroid therapy. Creatinine, compared to urea, may be disproportionately elevated in acute liver failure with renal failure.
- **Ca^{2+} , PO_4^{3-}** Acidemia increases ionized Ca^{2+} . Early stage of rhabdomyolysis may be associated with low Ca^{2+} . Later stages may be associated with hypercalcaemia. Hypercalcaemia and AKI: consider myeloma or sarcoidosis.
- **FBC** Anaemia suggests chronic or acute-on-chronic kidney disease. Low platelets suggest liver disease, HELLP (HUS, elevated liver enzyme, low platelet count) and sepsis. Blood film showing fragments [HUS, myeloma (left shift)]. ↑ platelets: inflammatory conditions, e.g. vasculitis (AAV). Eosinophilia: eosinophilic granulomatosis with polyangiitis (EGPA) and in a proportion of patients with interstitial nephritis.
- **Coagulation** Abnormal in DIC, liver disease, SLE, HELLP syndrome. PT and partial thromboplastin time (PTT) are normal in HUS/atypical HUS.
- **LFTs** Acute hepatitis, paracetamol OD, cirrhosis. ALP often ↑ in vasculitis.
- **LDH/HBD** ↑ in MAHA, e.g. HUS/TTP/DIC.
- **CK** Very high in rhabdomyolysis.
- **Blood cultures** Take in patients with AKI when sepsis is suspected.
- **Immunology** ANCA, anti-GBM, Igs, C3/C4, rheumatoid (Rh) factor, ANA, extractable nuclear antigen (ENA), double-stranded DNA (dsDNA), cryoglobulins, anticardiolipin, lupus anticoagulant, and anti-β₂-glycoprotein-1 antibodies (antiphospholipid syndrome).
- **ESR/CRP** CRP and ESR are elevated in vasculitis. CRP may be normal in SLE.
- **Protein strip** For paraproteins (myeloma, light chain disease). Free light chains and urine B₂ protein.
- **HIV, HBsAg, HCV Ab** Serology required for dialysis. HIV important cause of AKI, as well as hepatitis-associated renal disease.

Urine

- Inspect the urine yourself. Contact the renal registrar or microbiology technician on call to arrange urgent microscopy. Save urine for cytology if haematuria is the dominant symptom, and do urine dipstick for nitrites, protein, and blood.
- Send a specimen to microbiology for microscopy and culture.
- **RBC casts** suggest glomerulonephritis (refer to the renal physician urgently); **pigment casts** suggest myoglobinuria; **WBC casts** suggest acute pyelonephritis. *Excess eosinophils* in the urine are associated with interstitial nephritis.

- Urine B₂ protein, present in 75% of myeloma.
- *Urine electrolytes and osmolality*: these may help but do not replace careful clinical examination and are unreliable when diuretics have been given or in established AKI. They may be less reliable in the elderly when subclinical renal impairment may be present (see Box 4.2).

Other investigations

- USS: all patients with AKI should have an urgent renal USS to exclude obstruction and assess kidney size (small or asymmetric in acute-on-chronic failure), and blood flow on Doppler imaging. Immediate USS of the urinary tract when infected and obstructed kidney(s) is suspected (within 6h); USS within 24h when no identified cause of AKI or at risk of obstruction.
- CXR: look at the heart size (dilated, pericardial effusion), pulmonary vasculature (pulmonary oedema, Kerley lines), lung fields ('fluffy' shadows: oedema, haemorrhage in renal–pulmonary syndromes such as AAV).
- ECG: look for changes of hyperkalaemia (tented T waves, QRS broadening) and signs of myocardial ischaemia or pericarditis.

Box 4.2 Urinary electrolytes and osmolality in renal failure

Urine electrolytes are generally not very useful in clinical practice. A high urine osmolality (>550) with a low urine Na⁺ (<10mmol/L) indicates hypovolaemia.

Acute kidney injury: management

Hyperkalaemia

In general terms, the absolute K^+ concentration is less important than the effect on the cardiac-conducting tissue (tented T waves, broad QRS, flattened P wave; see Fig. 4.1). The risk of arrhythmias increases with K^+ values of 6.5mmol/L; treat urgently. The European Resuscitation Council Guideline definition of hyperkalaemia is defined as moderate (6.0–6.4) or severe (≥ 6.5 mmol/L). If hyperkalaemia is unexpected, with no ECG signs of hyperkalaemia, then repeat K^+ urgently. The ECG changes may be unpredictable and lead to sudden death.

If there are ECG changes or $K^+ > 6.5$ mmol/L (severe hyperkalaemia), contact the renal or intensive care teams.

- Record a 12-lead ECG; attach to a cardiac monitor.
- If the ECG shows signs of hyperkalaemia, give 10mL of 10% calcium gluconate IV, repeated every 5–10min until the ECG normalizes (patients may require up to 50mL). IV calcium does not lower the K^+ level but reduces cardiac excitability and has a duration of 30–60min.
- Insulin–glucose by IV infusion should be used in the treatment of severe hyperkalaemia ($K^+ \geq 6.5$ mmol/L) and may be used in the treatment of moderate hyperkalaemia ($K^+ 6.0$ – 6.4 mmol/L). Give 50mL of 50% glucose with 10U of soluble insulin over 15–30min, and monitor blood glucose; this should lower K^+ for several hours.
- Salbutamol 10–20mg via nebulizer can be used as adjuvant therapy to drive K^+ into cells in severe hyperkalaemia and may be used in moderate hyperkalaemia (use lower doses in patients with IHD). Salbutamol should not be used as therapy alone for hyperkalaemia.
- Give 50–100mL of 8.4% bicarbonate IV via a central line over 30min (or 500mL of 1.26% peripherally). Although this is often practically done, guidelines (Renal Association, 2012) suggest there is insufficient evidence to justify the routine use of sodium bicarbonate infusions.
- Furosemide 250mg IV over 1h if patient still passing urine.
- Polystyrene sulfonate resin enema (Calcium Resonium®) 30g increases gut losses of K^+ . Follow with 15g PO tds with regular lactulose. This takes 24h to work. Currently, there is no role for cation exchange resins in the emergency treatment of severe hyperkalaemia.
- Monitor serum K^+ frequently to assess response to treatment and to assess any rebound hyperkalaemia.
- Hyperkalaemia resistant to medical treatment is an indication for RRT.

Fluid balance

- Those patients with haemodynamic instability will need to be managed on HDU or ITU (see Box 4.3 for indications for dialysis).
- Measure weight, BP (supine and sitting or upright), and HR.
- Assess hydration (dry axillae, central skin turgor, mucous membranes, and JVP).
- Examine fluid and weight charts, and operation notes if applicable.

If volume-depleted

- If the patient is volume-depleted/postural hypotension, give a trial of volume expansion (500mL of colloid or normal saline) over 30min. Monitor urine output response.
- When adequately filled, reassess urine output. Do not give furosemide or a loop diuretic, unless the patient is clinically overloaded. Current

guidelines do not recommend the routine use of loop diuretics to treat AKI. Loop diuretics can be considered for the treatment of fluid overload or oedema while a patient's renal function is recovering or the patient is awaiting RRT. A meta-analysis of randomized controlled trials (RCTs) showed that furosemide is not associated with any significant clinical benefits in the treatment of AKI in adults and high doses may be associated with an ↑ risk of ototoxicity. Current recommendations state that dopamine should not be given to treat AKI.

- If hypotension persists (MAP <60mmHg), in spite of adequate volume replacement (i.e. CVP of >10cm), commence inotropic support (➡ Hypovolaemic shock, p. 333).

If fluid-overloaded

- Give O₂ to maintain SaO₂ >95%. Consider CPAP (➡ Continuous positive airways pressure, p. 827).
- Start IV nitrates (e.g. GTN 2–10mg/h IV).
- Give IV furosemide: 120mg–500mg, then infuse 5–10mg/h.
- Paracentesis if tense ascites is present (➡ Total paracentesis, pp. 842–3).
- Avoid opiates, although a single dose (e.g. 2.5mg diamorphine IV) may help relieve anxiety and breathlessness.
- If no response, consider urgent haemofiltration, dialysis, or lastly venesection (remove 250–500mL) (see Box 4.3).

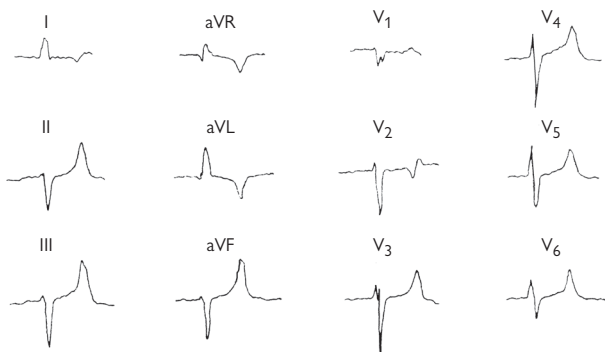


Fig. 4.1 Patients with hyperkalaemia develop tall tented T waves and a shortened QT interval. Later there is widening of the QRS complex and VT or VF.

Box 4.3 Indications for dialysis or haemofiltration

- Persistent hyperkalaemia refractory to medical treatment (K⁺ >6.5mmol/L).
- Fluid overload (e.g. refractory pulmonary oedema).
- Uraemic complications such as pericarditis (heralds the risk of tamponade; ➡ Acute pericarditis: assessment, p. 156–7).
- Refractory acidosis (arterial pH <7.15, bicarbonate <12mmol/L).
- Symptomatic uraemia with end-organ involvement (tremor, cognitive impairment, coma, fits).

Acute kidney injury: further management

Treatment of life-threatening hyperkalaemia, severe fluid overload, or dehydration takes priority (see Box 4.4) (➡ Acute kidney injury: management, pp. 298–9).

Correct other abnormalities

- **Acidaemia:** classically produces sighing respirations (Kussmaul's breathing) and may worsen hypotension (impaired cardiac function).
 - If pH is <7.2, give 100mL of 8.4% bicarbonate via a central line over 30min (or 500mL of 1.26% bicarbonate peripherally). Arrange urgent dialysis.
 - Correction can cause symptomatic hypocalcaemia.
- **Hyponatraemia:** usually dilutional (relative water excess). Management is discussed under on ➡ Hyponatraemia: management, p. 566.
- **Hyperphosphataemia** is more a problem of CKD and is related to dietary intake of PO_4^{3-} . Give oral phosphate binders with meals to lower PO_4^{3-} . Dialysis or haemofiltration will remove PO_4^{3-} .
- **Nutrition:** there is no role for protein restriction. Institute enteral or parenteral feeding early. In patients with DM, insulin requirements fall with renal impairment.
- **Sepsis:** common precipitant/complication of AKI. Culture blood, urine, and specimens from other potential sites of infection. Always consider infective endocarditis. Treat with appropriate antibiotics, remembering to adjust the daily dose in view of the renal impairment (septic shock is discussed under ➡ Sepsis syndrome and septic shock, pp. 336–7).

Further measures

The causes of AKI are listed in Box 4.1. Most cases are multifactorial, with volume depletion or hypotension, sepsis, and drugs (e.g. injudicious use of ACEIs and NSAIDs), urinary tract obstruction, and/or pre-existing chronic renal disease. It is essential to identify treatable conditions. Untreated, pre-renal causes will result in ATN.

Patients should be divided into those with pre-renal, renal, and post-renal AKI, using *clinical assessment*, *filling pressures* in ITU setting (CVP), and *USS*. While sepsis is included as a renal cause, much of the early deleterious effects (i.e. hypotension) are potentially reversible with appropriate management. The principles of further management are:

- **Optimize fluid balance:** there is no substitute for painstaking physical examination. Careful fluid balance charts and daily weights guide replacement. Limit fluid intake to total fluid output plus 500mL/day. The best sign of intravascular volume depletion is a postural drop in BP.
- **Intrinsic renal disease:** oliguria is reversed by restoration of circulating volume or BP but takes up to 8h to respond fully. It is important that fluid balance is optimized (CVP of 5–10cm, MAP of >75mmHg). If use of diuretics in those patients who are clinically overloaded fails to improve urine output, acute tubular injury is likely to be established, and the patient may require renal support.

- *Patients with severe portal hypertension and ascites:* may be oliguric (~250mL urine per day), with a concentrated urine virtually devoid of Na^+ due to severe renal vasoconstriction and avid reabsorption of Na^+ (urinary $\text{Na}^+ < 10\text{mmol/L}$). These patients may maintain normal plasma creatinine levels with preserved tubular function. They are often resistant to diuretics but may respond transiently to volume expansion. Beware of precipitating electrolyte or renal dysfunction by overdiuresis.
- *RRT, general points:* due to the altered kinetics of AKI and clearance by RRT, dose adjustment for medications will likely be necessary. Due to the risk of malnutrition, patients with AKI requiring RRT should be referred to a dietician. Trace elements and water-soluble vitamins should be supplemented, as required, due to losses by RRT (Renal Association AKI guidelines).
- *Vascular access:* all temporary dialysis lines should be inserted by experienced or supervised staff using US guidance. Generally, subclavian access is avoided due to the risk of stenosis potentially affecting future vascular access in those patients at risk of requiring permanent RRT. The duration of vascular access is as per local guidelines. With temporary access, there is a risk of exit site infections, as well as catheter-related bacteraemia.
- *Timing of RRT in AKI:* complex decision regarding the timing of initiation of RRT in AKI, with optimal timing of RRT not clear with trial data on early versus late initiation contradictory. Two previous prospective trials failed to demonstrate a benefit of $\uparrow$ intensity of RRT. For those patients with severe hyperkalaemia (refractory, $> 6.5\text{mmol/L}$), significant metabolic acidosis ($\text{pH} < 7.15$), uraemia, and fluid overload due to AKI, the benefits of RRT are clear. Those patients with MOF generally start RRT earlier than those patients with isolated AKI in the absence of other organ failure.

Box 4.4 Management key points: AKI

- Treat *hyperkalaemia* (if ECG changes or $K^+ > 6.5 \text{ mmol/L}$):
 - 10mL of 10% calcium gluconate IV.
 - 50mL of 50% glucose with 10U soluble insulin over 15min.
 - Nebulized salbutamol.
 - Contact the renal team and arrange for dialysis if appropriate.
- Treat *metabolic acidosis* (if pH < 7.2):
 - 50–100mL of 8.4% bicarbonate via a central line over 15–30min, or 1.26% sodium bicarbonate peripherally.
- Treat *pulmonary oedema*:
 - O_2 , consider CPAP.
 - IV GTN 2–10mg/h.
 - IV furosemide: 250mg over 1h, followed by infusion (5–10mg/h).
 - IV diamorphine (single dose of 2.5mg) relieves anxiety and breathlessness.
 - Haemofiltration or dialysis.
- Assess *hydration and fluid balance*: HR, lying and standing BP, JVP, skin turgor, chest auscultation, ? peripheral oedema, CVP, fluid and weight charts.
- *IV fluids* if volume-depleted: 500mL of colloid or 0.9% saline over 30min; assess response (i.e. urine output/CVP); continue fluids until CVP ~5–10cm. Inotropes if hypotension persists in spite of CVP of $> 10 \text{ cm}$.
- *Treatment of infection*: remember to adjust the dose of antibiotics in view of the renal impairment.
- *Stop the nephrotoxic drugs* (e.g. ACEIs and NSAIDs) and non-essential drugs.
- *Urine dipstick* and identify intrinsic renal disease, and refer for specialist renal input.
- *Relieve the obstruction*, e.g. urinary catheter, nephrostomies.
- *Optimize nutritional support*.
- *Identify and treat bleeding tendency*: prophylaxis with PPIs or H_2 -antagonist; transfuse if required (watch K^+), avoid aspirin.

Anuria

Anuria implies that there is no urine output.

Causes

- Obstructed urinary tract—bilateral ureteric or bladder outflow.
- Renal infarction—thromboembolic, renal artery injury (dissection, thrombosis).
- Rapidly progressive glomerulonephritis.
- Shock.
- Other causes of AKI may rarely cause anuria. ATN usually causes oliguria.

Assessment

Assess as for AKI. However, also:

- Ask specifically about symptoms of prostatism or haematuria (tumour) and backache (stones, aneurysm).
- Recent renal angiography or angioplasty (cholesterol embolization, renal infarction).
- Constitutional symptoms suggestive of glomerulonephritis.
- Has the patient previously lost a kidney?
- Does the patient have a renal transplant?
- Examine for palpable bladder, enlarged prostate, or other pelvic masses. Insert a urinary catheter to exclude retention. A bladder scan will also demonstrate urinary retention.

Management

(See  Acute kidney injury: management, pp. 298–9.)

If patient is anuric:

- General measures such as careful assessment of fluid balance and appropriate fluid resuscitation. Antibiotics if an obstructed, infected system is suspected. If fluid-overloaded/refractory hyperkalaemia, will require RRT.
- If the bladder is empty, an urgent USS is needed to confirm renal perfusion and exclude urinary tract obstruction (or obstruction of a solitary functioning system). Antegrade imaging can determine the level of obstruction, but consult with the urologists and radiologists.
- Absence of hydronephrosis does not exclude obstruction.
- USS with Doppler of renal vessels. Arrange a CT scan $\pm$ contrast if USS normal and dissection is suspected. A non-contrast CT will demonstrate an obstructing stone.
- If no evidence of obstruction (one cannot exclude acute obstruction on USS), an isotope renogram will provide further information on renal perfusion. Nuclear medicine imaging can also determine if non-obstructive hydronephrosis is present.
- Involve the urologists for further management of obstruction.

Interstitial nephritis

This is caused by inflammatory cell infiltration of the renal interstitium, usually induced by drugs (NSAIDs, penicillin, cephalosporins, sulfonamides, allopurinol, rifampicin, mesalazine, interferon, PPIs), autoimmune conditions (sarcoid, SLE, IgG4-related disease), and some infections (e.g. *Legionella*, *Leptospirosis*, viral). Other causes include DM, sickle-cell disease, reflux nephropathy, and renal transplant rejection. Drugs are the most common cause, and it is not a dose-dependent effect.

Presentation

Non-oliguric AKI. Fever, rash, eosinophilia (triad not commonly occurring), and urinary eosinophils. Precipitating cause usually precedes renal impairment by a few days to 2 weeks (very variable). Usually low-grade proteinuria.

Diagnosis

Renal biopsy.

Treatment

Stop the offending drug. Use of steroids in this setting remains controversial, with no RCTs performed and published studies demonstrating variable benefits. However, many continue to give steroids. Mycophenolate mofetil has also been given to patients in whom glucocorticoid therapy may have failed.

Rhabdomyolysis

This is the development of AKI due to extensive muscle damage and resulting muscle cell death and the release of myoglobin; ~7% of all cases of AKI. For causes, see Box 4.5.

Presentation

- Most cases occur following muscle trauma (e.g. crush syndrome) or severe physical exertion (e.g. marathon running or military training).
- Prolonged immobility (e.g. after drug OD and coma) may result in pressure necrosis of the muscles.
- Malignant hyperthermia or malignant neuroleptic syndrome.
- Drugs (e.g. statins) and infections.
- Symptoms include swollen tender muscles, dirty red-brown urine (like Coca-Cola® mixed with urine), and/or oliguria.
- Myoglobin is present in muscle as ferrous (Fe^{2+}) myoglobin, and myoglobin is deposited in the kidney as ferric (Fe^{3+}) myoglobin. Further oxidation of myoglobin by hydroperoxides generates a potent oxidizing species ferryl (Fe^{4+}) myoglobin that causes renal injury. Obstruction of the tubules also occurs. Alkalinization works by stabilizing ferryl myoglobin and making it less reactive.

Investigations

- *U&Es*: typically marked increase in serum K^+ , $\uparrow$ creatinine:urea ratio.
- Ca^{2+} : low Ca^{2+} occurs in a significant proportion of patients, with deposition of Ca^{2+} into bone. Later on, hypercalcaemia can result.
- PO_4^{3-} : high as PO_4^{3-} released during muscle cell death.
- *Urate*: usually $\uparrow$ with tissue necrosis, also $\downarrow$ excretion.
- *LFTs*: AST very high—from skeletal muscle.
- *CK*: very high (up to 1×10^6 U/L).
- *LDH*: elevated.
- *ABG*: metabolic acidosis, hypoxic if there is associated acute lung injury (trauma) or infection.
- *Urine*: the urine looks red-brown. Urinalysis is positive for blood (myoglobin tests positive), but no RBC seen on microscopy. Urinary myoglobin is diagnostic.
- *Miscellaneous*: FBC, glucose, blood cultures, ESR, CRP, serum for toxicology $\pm$ virology, plasma myoglobin, ECG. Serum looks clear (cf. haemolysis), as myoglobin does not bind haptoglobins and is filtered by the glomerulus and then excreted.

Management

Patients are often febrile, volume-depleted, and unwell. Myalgia may be present. The priorities are:

- Hyperkalaemia needs urgent treatment (➡ Acute kidney injury: management, pp. 298–9).
- Volume replacement: to prevent the risk of AKI due to rhabdomyolysis, aggressive fluid management is required, often with several litres of fluid in the first few hours. To prevent fluid overload, especially in those oliguric patients, regular assessment of fluid balance is required, with documentation of urine output.

- Alkaline diuresis with 1.26% sodium bicarbonate or 8.4% centrally (➡ Aspirin, pp. 748–9): alkalization stabilizes the oxidizing form of myoglobin. It is usually effective within the first 8h. Test the urine regularly with pH strips to maintain urine pH >6.5, with regular monitoring of Ca^{2+} and bicarbonate level in the serum.
- Analgesia: avoid NSAIDs—use opiate analgesia, if required.
- Evidence of compartment syndrome: refer for a surgical opinion. Fasciotomies or debridement of necrotic tissue may be needed for compartment syndrome.
- Avoid Ca^{2+} infusion to treat hypocalcaemia: it may cause metastatic calcification in damaged muscle and cause further tissue necrosis. However, IV Ca^{2+} is indicated for patients with severe hyperkalaemia.
- Treat the underlying cause (see Box 4.5).
- Dialysis or haemofiltration may be necessary for the short term, but full recovery of renal function is likely.

Box 4.5 Causes of rhabdomyolysis

- Crush injury.
- Severe exertion, heat stroke.
- Prolonged convulsions.
- Prolonged immobility.
- Polymyositis or viral myositis.
- Malignant hyperpyrexia.
- Acute alcoholic binge.
- Drugs, e.g statins.
- McArdle's syndrome.
- Hypokalaemia.
- Carbon monoxide (CO) poisoning (➡ Carbon monoxide, p. 753).
- Burns.
- DKA (➡ Diabetic ketoacidosis: assessment, p. 546–7).
- Ecstasy abuse (➡ Recreational drugs: stimulants, p. 766–7).
- Snakebite.
- Electric shock.
- Neuroleptic malignant syndrome (➡ Neuroleptic malignant syndrome, p. 604–5).

Hepatorenal syndrome

This is defined as the onset of renal failure or AKI in patients with severe liver disease in the absence of renal pathology. It may occur in either cirrhosis or acute liver failure. It may be characterized by a low urine Na^+ ($<10\text{mmol/L}$), but this is not a criterion in the diagnosis. It may be acute (type 1) occurring within 2 weeks, or insidious in development in patients with refractory ascites (type 2). Renal vasoconstriction occurs in order to maintain renal perfusion and GFR.

Presentation

- An increase in serum creatinine is most commonly found as an incidental finding during biochemical screening of patients with ascites (cirrhosis) or jaundice (especially common in alcoholic hepatitis). Significant haematuria and proteinuria are not features.
- Causes of renal failure in cirrhosis that should be excluded before a diagnosis of HRS is made include hypovolaemia, shock, intrinsic renal disease, and concomitant use of nephrotoxic drugs.
- The most common precipitant of HRS in patients with advanced liver disease is sepsis; 30% of patients with SBP develop HRS. GI bleeding is an additional precipitant.

There are many causes of renal failure and liver disease which are *not* synonymous with HRS, and should be actively excluded. These include:

- Hypovolaemia: caused by bleeding, overdiuresis, or post-paracentesis circulatory dysfunction.
- Sepsis.
- Nephrotoxic drugs given to patients with liver disease (e.g. gentamicin).
- Chronic viral hepatitis (HBV or HCV) with glomerulonephritis.
- IgA nephropathy.
- Leptospirosis (marked hyperbilirubinaemia, liver enzymes near normal).
- Paracetamol OD.
- Rhabdomyolysis may mimic liver disease and HRS by causing DIC (high PT) and high AST (muscle injury).

Investigations

See 🔄 Acute kidney injury: investigations, pp. 296–7.

Management

- Exclude other causes of renal failure in liver disease (see 🔄 'Presentation' above).
- $\pm$ insert a urinary catheter, and monitor urine output.
- Volume challenge; stop diuretics; 20% IV albumin.
- Ideally CVP should be monitored to help in the management of fluid balance, and particularly to prevent volume overload.
- Broad-spectrum antibiotics: based on current evidence, terlipressin should be considered to be the first-line therapeutic agent for patients presenting with type 1 HRS. Contraindicated in patients with IHD and peripheral vascular disease. Most studies have used terlipressin (initially 0.5–1mg every 4h), together with albumin therapy (1g/kg day 1,

then 40g daily). Terlipressin and albumin therapy leads to reversal of type 1 HRS in ~40% of patients but has no clear benefit on 3-month survival. If terlipressin is unavailable, or patients require critical care, use NA (1–10 micrograms/min).

- If there is tense ascites, total paracentesis will decrease the renal venous pressure and enhance renal blood flow (➡ Total paracentesis, pp. 842–3), but there are no data on efficacy on outcome.
- In patients with type 2 HRS, TIPS may improve ascites and renal function.
- Haemofiltration or dialysis: patients tolerate haemofiltration better than haemodialysis.
- Patient with HRS and a reversible cause of liver failure or those patients awaiting liver transplantation should be offered RRT.
- RRT should be avoided in those patients without a reversible component or who are not candidates for liver transplantation.
- Patients with HRS should be discussed with a liver transplant centre. HRS can be reversed by liver transplantation, but the prognosis from liver transplantation is worse in this group.
- Hyperkalaemia and acidosis are rarely a problem.

For management, see Box 4.6.

Box 4.6 Management key points: HRS

- IV fluids (1L Hartmann's solution over 2h ± albumin).
- Stop all diuretics.
- Antibiotics (e.g. cefotaxime + metronidazole) after cultures.
- Terlipressin (0.5–1mg IV every 4–6h) with albumin (1g/kg and 40g daily thereafter, or NA (1–10 micrograms/min) if MAP <75mmHg. Assess response by urine output.
- Haemofiltration or dialysis, if appropriate.
- Paracentesis for tense ascites (no data available on efficacy).
- Monitor urine output/fluid balance.
- Hyperkalaemia and acidosis are rarely a problem.
- Discuss with a liver transplant centre.

Acute upper urinary tract infections

Infection of the upper urinary tract may result in acute pyelonephritis, renal abscess, pyonephrosis, or perinephric abscess (see Fig. 4.2). Infection with obstruction causes rapid tissue destruction, unless the obstruction is relieved. This is a urological emergency.

Predisposing factors

- Either an ascending infection or haematogenous spread.
- Organisms: *Escherichia coli* (60%), *Proteus* (20%), *Enterococcus faecalis* (10%), *Klebsiella* (5%).
- ♀ (short urethra).
- Renal stones.
- Bladder catheter.
- Chronic liver disease.
- Structural abnormality of the renal tract.
- Pregnancy.
- DM.
- IV drug abuse.
- IE.
- Renal transplantation.
- Immunosuppression.

Presentation

- Classical symptoms are loin pain, fever, and rigors.
- Non-specific symptoms may predominate, e.g. nausea, vomiting, anorexia, malaise, confusion, or weakness.
- Up to 75% have preceding lower urinary tract symptoms (frequency, urgency, dysuria). There may be associated haematuria.
- Severe bilateral pyelonephritis or acute-on-chronic pyelonephritis may result in AKI.
- A preceding history of intermittent loin pain may imply intermittent obstruction with pyonephrosis. Renal abscesses occur with IV drug use, endocarditis, or skin infections.
- Ask specifically about any predisposing factors.
- Signs include fever, abdominal or loin tenderness, a palpable mass in the loin, and, with severe infection, scoliosis, hypotension, and shock (septicaemia).
- Symptoms and signs may be difficult to distinguish from pneumonia or other causes of an acute abdomen (e.g. cholecystitis, diverticulitis).

Investigations

- Urinalysis commonly shows blood and protein. Urine nitrite is often positive. Pyuria usually present. WBC casts may be seen on microscopy. Culture may be negative in infections confined to the renal cortex.
- All patients should have U&Es (for renal dysfunction, dehydration, and acute-on-chronic failure), glucose, FBC (anaemia, leucocytosis), and blood cultures.
- AXR: stones, soft tissue mass, or loss of psoas line on affected side.
- USS to exclude obstruction and delineate renal and perirenal collections. Non-contrast CT will demonstrate structural abnormalities, calculi, and renal abscesses.

Management

(See Box 4.7.)

- Stabilize the patient: resuscitate severely ill patients with IV fluids $\pm$ inotropes, guided by CVP and BP (see Box 4.7).
- Give IV antibiotics. The choice of antibiotics may depend on previous culture results, as well as local guidelines. Discuss with microbiology for advice. Continue antibiotics for 7–14 days.
- Organize drainage of infected and obstructed urinary system.
- Fluid balance: maintain high fluid intake (e.g. 3L/24h). Monitor fluid balance and urine output carefully for the first 48–72h.
- Analgesia: try opiates. Avoid NSAIDs in AKI.
- Pyonephrosis, renal or perinephric abscess: requires urgent advice—contact the urologists. Save a sample for MC&S.
- When patient recovered, investigate for any underlying cause: flexible cystoscopy, investigation of bladder emptying, and imaging such as CT kidneys, ureters, and bladder (KUB). Dimercaptosuccinic acid (DMSA) renal scan will demonstrate scarring.

Box 4.7 Management key points: acute pyelonephritis

- Analgesia.
- IV fluids (if dehydrated); maintain high fluid intake.
- IV antibiotics: cefuroxime or ciprofloxacin may also be used; give a bolus of gentamicin as you initiate treatment. Modify antibiotics when culture/sensitivity results are known.
- Monitor BP, fluid balance, and urine output.
- Contact the urologists if pyonephrosis and renal/perinephric abscesses are suspected.
- Investigate for an underlying cause (CT KUB, cystoscopy, urodynamics, DMSA).

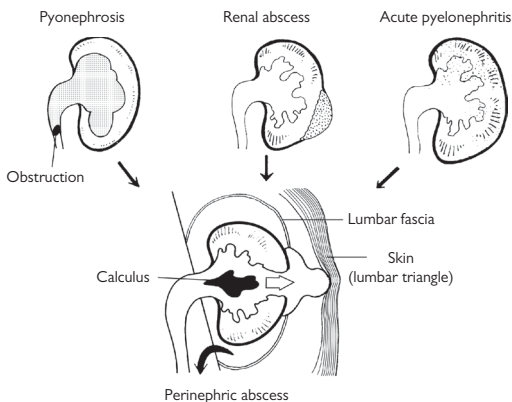


Fig. 4.2 Patterns of renal infections.

Renal colic and renal stones

Spasmodic pain radiating from loin to groin is usually due to stones or blood clots (see Box 4.8). ~2–3% of the population have a stone in the upper urinary tract. Pain can also be caused by a sloughed papilla, secondary to DM, sickle-cell disease, or analgesics.

Presentation

- May be painless or generalized abdominal pain.
- Pain: the site of the pain may vary; stones in the renal pelvis cause dull loin ache; ureteric stones produce severe colicky pain, often of sudden onset, radiating from loin to groin; bladder stones cause suprapubic and perineal or testicular ache.
- Haematuria (often frank) may be the only feature.
- With severe pain, the patient will be restless, sweaty, pale, nauseated, and very distressed.
- Is there a history of previous episodes? Ask about UTIs, previous stones, fluid intake, occupation, residence in hot climates, dietary intake, symptoms of hypercalcaemia, or family history of stone disease. Risk of oxalate stones with short bowel or gastric bypass surgery. History of indinavir.
- On examination, note any fever, abdominal tenderness (especially loin or subcostal), or palpable kidneys. Do not miss a leaking abdominal aortic aneurysm (AAA) that may be producing similar symptoms.

Investigations

- Bloods: U&Es (for renal dysfunction), glucose, and FBC (for Hb, WCC).
- Urine: dipstick urinalysis for blood and formal microscopy for crystals, pyuria, and bacteria. Culture for infection.
- AXR: >90% of renal stones are radio-opaque. Most, but not all, stones can be detected on a plain AXR.
- Non-contrast CT: demonstrates stones, as well as any obstruction. First choice of investigation.
- US may miss some stones and is less sensitive than CT.
- Tests to consider include: serum Ca^{2+} [parathyroid hormone (PTH) if Ca^{2+} high] and urate, and 24-h urine for pH, Ca^{2+} , PO_4^{3-} , oxalate, uric acid, and citrate to detect a stone-forming metabolic defect.

Management of acute renal colic

- Analgesia: opiates may be required.
- High fluid intake.
- Beware of infection above the stone and pyonephrosis (see Fig. 4.2). If there is fever, bacteriuria, or obstruction, treat empirically (according to local guidelines/microbiology advice) until culture results are known, and decompress any obstruction.
- Stones with infection or obstruction require urological management such as ureteroscopic extraction or extracorporeal shock wave lithotripsy. Retrieved stones should be analysed for their composition.

Prognosis

~60% of all stones will pass (depending on the location and size of the stone) (half of these within 48h). ~30% will require surgical removal, and 10% will recur. The risk of idiopathic stone recurrence is altered slightly by diet but is ↓ by a high fluid intake (>1.5L/day leads to a 6-fold decrease). It is important to control hypercalciuria if present (low-calcium diet, thiazide diuretics), treating hypercalcaemia if present (➡ Hypercalcaemia, pp. 572–4), urinary alkalization (hyperuricaemia, renal tubular acidosis, cystinuria), urinary acidification to pH <5.5, allopurinol (urate stones), or penicillamine (cystine stones). Patients with staghorn calculus are recommended to undergo a surgical procedure to remove the stone.

Box 4.8 Causes of renal colic

Renal stones

Usually divided into:

- **Radio-opaque** (90%): contain Ca^{2+} or Mg^{2+} , e.g. calcium oxalate (hypercalciuria, hypercalcaemia, dehydration, renal tubular acidosis, medullary sponge kidney, hyperoxaluria), calcium phosphate (as before and UTIs), magnesium ammonium phosphate (UTIs with urease-positive organisms, e.g. *Proteus*). Cystine stones are 'semi-opaque' due to their sulfur content.
- **Radiolucent**: urate or xanthine, or rarely 2,8-dihydroxyadenine.

Indinavir crystal deposition (HIV drug)

Renal papillary necrosis

- DM, sickle-cell disease, analgesic nephropathy. Pain occurs when a papilla 'sloughs' into the ureter.

Blood clots

- Due to trauma, tumour (parenchymal or urothelial), bleeding diathesis, or polycystic kidney disease.

Haematuria

History

Haematuria is either visible and symptomatic or microscopic and asymptomatic.

- Severity of haematuria: pink urine, frank blood, or clots?
- Timing of haematuria: bleeding occurring at start or end of micturition suggests bladder neck, prostate, or urethral source. Blood mixed with the stream suggests a source higher in the urinary tract.
- History of trauma: even seemingly minor trauma can cause bleeding from congenital lesions of the urinary tract.
- Unilateral loin pain: consider calculi, tumour, cystic disease, or hydronephrosis. Painless haematuria suggests neoplasm.
- Disturbance of micturition: frequency, urgency, dysuria, hesitancy, poor stream, and dribbling suggest cystitis. Bleeding and pain at the end of the stream is typical of a bladder stone.
- Constitutional symptoms: sore throats, arthralgia, malaise, and rash may indicate glomerulonephritis. AF is associated with renal emboli. Fever, dysuria, or abdominal pain may indicate infection. Bruising or other bleeding may indicate a bleeding diathesis.

For causes of haematuria, see Box 4.9.

Physical examination

- *General examination*: hypertension (chronic or acute renal disease), irregular pulse or heart murmurs (source of emboli), anaemia, bruising or purpura, oedema, or pleural effusions.
- *Urinary tract examination*: loin or abdominal tenderness, renal mass, pelvic mass, prostate enlargement, testes. Urine microscopy.

Investigations

- *Urinalysis* Positive result seen with myoglobinuria (➡ Rhabdomyolysis, pp. 306–7) and haemoglobinuria. Proteinuria suggests renal pathology.
- *Microscopy* RBC casts or dysmorphic red cells suggest a glomerular origin. WBC casts suggest pyelonephritis. Other findings include crystals (stone disease), ova (schistosomiasis), and malignant cells.
- *FBC* Thrombocytopenia and anaemia (haemolysis, leucocytosis) may indicate infection.
- *U&Es* For renal function.
- *Clotting* For coagulopathy.
- *G&S* If post-traumatic or severe.
- *Immunology screen* If glomerulonephritis is suspected. Refer to the renal team.
- *US* May diagnose polycystic disease, ureteric obstruction by stone or tumour, or gross renal abnormalities.
- *CT scan* May demonstrate stones, hydronephrosis, renal injury or tumour, cystic disease, or urothelial tumour.
- *Cystoscopy* To exclude other causes of bleeding from the lower urinary tract. Should be performed in patients with macroscopic haematuria or undiagnosed microscopic haematuria.

Management

- Admit patients with:
 - Post-traumatic haematuria (refer to urology).
 - Severe unexplained haematuria (including bleeding diathesis), especially if there is clot retention. Insert a large (22G) triple-lumen urinary catheter for continuous bladder irrigation with monosol (not glucose) to wash out clots.
 - Haematuria, proteinuria, and renal impairment suggest glomerulonephritis. Arrange for an urgent renal referral and biopsy.
 - Severe infection, e.g. pyelonephritis. Commence antibiotics after taking cultures.
- Pain relief (pethidine 25–50mg IV, with an antiemetic). Propantheline bromide 15mg tds PO relieves painful bladder spasm of haemorrhagic cystitis and clot retention (may cause urinary retention).
- Correct any bleeding diathesis (FFP or vitamin K for warfarin).

Box 4.9 Causes of haematuria

- | | |
|----------------------|---|
| • Trauma | Blunt and penetrating injuries, iatrogenic [e.g. recent transurethral resection of the prostate (TURP) or renal biopsy], severe exercise, foreign body. |
| • Stones | Renal, ureteric, or bladder. |
| • Infections | Pyelonephritis, haemorrhagic cystitis, acute prostatitis: bacterial, TB, or parasitic (e.g. schistosomiasis). |
| • Tumours | Urothelial, renal parenchymal, prostatic. |
| • Bleeding diatheses | Haemophilia, thrombocytopenia. |
| • Renal pathology | Glomerulonephritis, renal arterial emboli, renal vein thrombosis. |
| • Drugs | Anticoagulants, cyclophosphamide, penicillamine. |
| • Congenital | Polycystic disease, sickle-cell disease (papillary necrosis), Alport's syndrome, hydronephrosis. |

NB Discoloured urine may also be due to beetroot, porphyria, rifampicin, co-danthramer, and vegetable dyes.

Renovascular disease

Renal artery stenosis may be atherosclerotic (common in the elderly and diabetics), with excessive activation of the renin–angiotensin–aldosterone axis and resultant hypertension, or fibromuscular dysplasia (10%) (young patients). Fibromuscular dysplasia occurs in young patients, usually ♀, and may involve other vascular beds such as peripheral, coronary, or cerebral. Renal artery stenosis should be considered in all patients with:

- Flash pulmonary oedema (sudden, unexpected onset).
- Peripheral vascular disease, aortic dissection, and type 2 diabetes.
- Unequal kidneys on USS.
- Acute deterioration in renal function following the initiation of ACEI.
- Hypertension/coronary or carotid artery disease.
- Complete anuria in renovascular disease in a solitary kidney with an occluded artery.
- Patients with hypokalaemia.

Investigations

- USS: to look at renal size and asymmetry, and Doppler flow through the renal arteries.
- Isotope renogram.
- Magnetic resonance angiography (MRA) CT angiography: risk of contrast nephropathy.
- Be guided by your local radiologists.
- Digital subtraction angiography is sometimes used.

Management

- Avoid NSAIDs.
- Lipid-lowering therapy with statins.
- Recent trend by nephrologists to carefully introduce angiotensin blockade to treat hypertension, with gradual introduction and withdrawal if there is a significant decline in GFR.
- Diuretics due to salt and water retention.
- Refer to a dedicated team of interventional radiologists/vascular/nephrology if there is >70% stenosis with intractable hypertension (>5 drugs) and flash pulmonary oedema with declining renal function. The ASTRAL trial suggests that patients do *not* benefit from stents with respect to improving BP control. The CORAL trial did not demonstrate benefit in stenting in the prevention of cardiovascular or renal events. However, a small subset of high-risk patients may benefit.
- Fibromuscular dysplasia can be successfully managed with angioplasty in symptomatic patients.
- Stenting may permit the use of angiotensin blockade in previously intolerant patients.
- Mortality rate is ↑ in patients with atherosclerotic renovascular disease, with most dying from their associated IHD.

Cholesterol embolism

Most commonly seen in arteriopathies after manipulation of vasculature (e.g. angiography) and is followed by AKI. Usually silent. There is partial occlusion of small- and medium-sized arteries, resulting in ischaemic atrophy. More florid presentation includes: widespread purpura (livedo reticularis), dusky and cyanotic peripheries with intact pedal pulses, GI bleeding/ischaemia, myalgia, and AKI. It can be spontaneous or follow therapy with heparin or warfarin.

Diagnosis

Eosinophilia, renal impairment, hypocomplementaemia, ESR, ANCA negative. Urinary sediment is usually benign; mild proteinuria may be seen. Renal biopsy shows cholesterol clefts.

Management

The renal impairment is usually irreversible or only partially reversible [in contrast to ATN and contrast-induced nephropathy (CIN)]. Anticoagulation is contraindicated. Treatment is supportive.

Contrast-induced nephropathy

This is an acute impairment of renal function, which follows exposure (within 3 days) to radiocontrast materials. Defined as an increase in creatinine of $44.2\mu\text{mol/L}$ or a 25% increase in creatinine from baseline value. Incidence in an unselected population is 2–7% but increases to 25% if renal function is already impaired. Pre-expand the plasma volume with normal saline or sodium bicarbonate. In patients at risk of CIN, an alternative to contrast in vascular angiography studies is carbon dioxide. Higher risk of CIN following coronary angiography compared to enhanced CT scans, as well as higher risk following intra-arterial administration compared to venous administration.

Risk factors

- Chronic kidney disease ($\text{eGFR} < 60\text{mL/min/1.73m}^2$).
- Renovascular disease.
- Proteinuria (increases risk 3-fold).
- DM (risk depends on renal function (chronic kidney disease and DM risk of 25%).
- CCF.
- Recent MI.
- Multiple myeloma.
- Dehydration/hypovolaemia.
- Sepsis.
- Concomitant nephrotoxins (e.g. gentamicin, NSAIDs, amphotericin, high-dose loop diuretics).
- Age (> 75 years).

Management

There is no specific treatment. Prevention is the best policy.

- Monitor renal function 48–72h following contrast.
- Ensure good hydration pre-procedure (give patients who are at risk IV fluids pre-procedure).
- Avoid high-osmolar contrast media.
- Use minimal amounts of contrast.
- Stop nephrotoxic drugs (especially NSAIDs) peri-procedure. Avoid diuretics.
- Stop metformin 48h before contrast (if $\text{GFR} < 60\text{mL/min/1.73m}^2$).
- Continue IV fluid following procedure for 12h.
- Acetylcysteine is no longer thought to be effective. Conflicting results in different trials and meta-analysis.
- ↑ risk of adverse outcomes following an episode of CIN AKI.
- No current evidence for RRT following contrast in patients with chronic kidney disease to prevent contrast nephropathy.

Urine appearance

Typical urine is pale yellow to amber in colour. Other colours do not necessarily imply pathology:

- *Red*: haematuria, haemoglobinuria, beetroot, rifampicin, senna, porphyrinuria.
- *Brown*: haematuria, haemoglobinuria, myoglobinuria, jaundice, chloroquine, carotene.
- *Black*: haematuria, haemoglobinuria, myoglobinuria, alkaptonuria (black on standing).
- *Green*: triamterene, propofol.
- *Darkening on standing*: porphyrinuria [fluorescence in ultraviolet (UV) light], metronidazole, imipenem, or cilastatin.

Renal–pulmonary syndromes

Consists of rapidly progressive glomerulonephritis with alveolar haemorrhage. There are several underlying causes of renal–pulmonary syndrome, with a variety of presentations. Patients may deteriorate rapidly with respiratory/renal failure and require ITU. Early diagnosis is key to allow prompt treatment and recovery of renal function. The most common causes are AAV and anti-GBM disease. Rarer causes include SLE, cryoglobulinaemic vasculitis, IgA vasculitis, and scleroderma.

Presentation

- May present acutely over a few days.
- Haemoptysis, shortness of breath, hypoxia, and cough may be present.
- Oliguria or anuria AKI.
- Extrarenal features may be present: fever, rash, arthralgia, depending on the underlying diagnosis.
- GPA may be characterized by upper airway and ENT involvement: epistaxis, nasal symptoms.
- EGPA: asthma, nasal polyps may be present.

Investigations

- *FBC*: anaemia, ↑ platelets in AAV and anti-GBM disease, eosinophilia in EGPA.
- *U+E*: AKI.
- *LFTs*: ↑ ALP.
- *CRP*: elevated.
- *Urine dipstick*: blood and protein with glomerulonephritis.
- *Immunology tests*: ANCA, anti-GBM, complement, cryoglobulinaemia (consider hepatitis), rheumatoid factor, ANA, dsDNA.
- *Virology*: hepatitis, HIV.
- *CXR*: sensitive, but not specific, for pulmonary haemorrhage. Some patients may not demonstrate alveolar shadowing.
- *High-resolution CT (HRCT)*: may demonstrate ground-glass changes.
- *PFTs*: measurement of elevated transfer factor.

Diagnosis

- Renal biopsy to diagnose glomerulonephritis.

Treatment

- May require ITU for respiratory support/renal support.
- Immunosuppression consisting of steroids (initially 60mg/day, followed by gradual tapering over 6–9 months) and cyclophosphamide (usually IV over 3–6 months). Azathioprine maintenance therapy used in AAV after completion of cyclophosphamide [measure thiopurine methyltransferase (TPMT) levels]. Mycophenolate can also be used.
- Rituximab-based regimes are also used during induction and maintenance treatment.

- Plasma exchange in those patients with pulmonary haemorrhage or severe glomerulonephritis (awaiting publication of the PEXIVAS trial).
- Prophylaxis against PCP (co-trimoxazole often used), gastric and bone protection.

Prognosis

- GPA has better survival than microscopic polyangiitis.
- Dialysis may be temporary or permanent.
- Those patients with anti-GBM disease presenting with dialysis-dependent renal failure have very low rates of renal recovery and may not be treated with immunosuppression to treat the renal lesion.
- Patients should be managed in specialist centres.

Nephrotic syndrome

In adults, causes:

- minimal change disease (MCD) (15%).
- focal segmental glomerulosclerosis (FSGS) (35%).
- membranous nephropathy (35%).
- membranoproliferative glomerulonephritis (MPGN) (5%).
- other (10%).

Nephrotic syndrome consists of significant proteinuria (3g/24h), with low albumin, high cholesterol, and oedema. Patients are prothrombotic and may present with DVT/PE or renal vein thrombosis.

General measures

- Assess as per AKI: request full immunology screen, virology; investigate for paraprotein.
- Drug history important: NSAIDs, lithium, pamidronate, heroin.
- USS: workup for renal biopsy.
- Patients may have significant oedema and require admission for IV diuresis with furosemide. This can be given as a 24-h infusion (250–500mg over 24h).
- Severe oedema; consider adding in metolazone 2.5mg—initially alternate days.
- Fluid-restrict and daily weights.
- Lying and standing BPs.
- Monitor input and urine output and HR, with care to avoid overdiuresis and contraction of intravascular compartment resulting in further AKI.
- Prophylactic heparin due to prothrombotic tendency (unless a contraindication: stop 24h before a renal biopsy).
- Statin.
- If hypertensive, ACEI or ARB will have an additional anti-proteinuria effect.
- Rapid decline in renal function; consider renal vein thrombosis.
- Prepare for renal biopsy.

Minimal change disease

- Microscopic haematuria present in 10–30%. Chronic kidney disease/end-stage renal failure not typically seen. AKI may be seen in 20–25% of patients, typically in older patients.
- Usually idiopathic.
- Drug history important: NSAID, lithium use.

FSGS

Genetic testing can be performed in patients presenting early on in life and in childhood. May be primary/idiopathic, or secondary—mutations (actinin), associated with virus infections (HIV, parvovirus B19), medications (pamidronate, lithium), hyperfiltration (obesity, diabetes), malignancy (lymphoma). Previous glomerulonephritis resulting in scarring.

Membranous nephropathy

Sixty to 80% of patients present with nephrotic syndrome, with microscopic haematuria in 50%. Over 70% of patients with primary membranous nephropathy are positive for anti-phospholipase A2-receptor antibody. Many secondary causes to consider include: hepatitis B, malignancy, and SLE. Spontaneous remission occurs in up to 30%.

MPGN

Classification based on renal biopsy findings (presence or absence of Ig and/or complement staining). Investigate for paraproteinaemias, autoimmune disease, and infections. Treatment is aimed at the underlying cause.

Treatment

Depends on the underlying cause.

- MCD: prednisolone 1mg/kg until complete remission, then slow taper. Over 50% of adults will relapse, requiring repeated steroids. With frequent relapses or steroid dependency, a calcineurin inhibitor (CNI), e.g. tacrolimus, may be added. Cyclophosphamide for 8 weeks has also been used. Rituximab may also decrease relapse rate.
- FSGS: prednisolone high dose or CNI. Some patients may not respond to treatment and progress to end-stage renal failure. FSGS may reoccur in renal transplant.
- Membranous nephropathy: observe for 6 months, due to a proportion of patients entering spontaneous remission. Those with nephrotic-range proteinuria/or nephrotic syndrome with life-threatening features at presentation would be treated. Treatment consists of steroids and an alkylating agent or CNI therapy. Rituximab has also been used.

Emergencies in dialysis patients

These patients are managed within the setting of a specialist renal unit.

General measures

- Great care with fluid administration: assessment of fluid balance can be a challenge.
- If patients are active on the renal transplant list, avoid unnecessary blood transfusions which may result in sensitization.
- Avoid K^+ -containing IV fluids, as may accumulate, resulting in hyperkalaemia.
- May be on immunosuppression due to underlying autoimmune disease or previous transplantation: may require monitoring of immunosuppressant drug levels and changes in dose of corticosteroids.
- Dialysis patients are relatively immunosuppressed: low threshold to investigate sepsis and antibiotics.
- Dietary restrictions: adherence to the renal diet.
- Avoid certain drugs: opiates with renal clearance as can accumulate and cause respiratory depression, and NSAID risk of GI bleeding.
- Save residual renal function: some patients still have residual function, which is crucial in fluid balance. Avoid contrast CT (unless necessary); no NSAIDs, and avoid nephrotoxic medications (gentamicin).
- Dialysis patients presenting with fluid overload need urgent RRT. Either dialysis in a renal unit or may require ITU. Those patients who are hypoxic/with high O_2 demands are not safe for transfer to a renal unit and require critical care to be stabilized.
- Be aware of high risk and mortality of cardiovascular events. The trend in troponin is useful.
- Hyperkalaemia: both insulin–glucose and calcium gluconate are temporary measures. The patient will require urgent dialysis.
- Early discussion with the nephrologist, and transfer to a renal unit if medically safe to do so.

Haemodialysis

Fever in a haemodialysis patient and a tunnelled haemodialysis line

- *History*: ask about cough, back pain, fevers, pain/redness over access site, and fevers during dialysis. Important to know if the patient has a history of immunosuppression (previous transplants or underlying autoimmune disease).
- *Examination*: inspect access site; assess for signs of endocarditis, spinal tenderness. Assess for meningism/chest signs.
- *Investigations*: swabs from exit site, peripheral blood cultures, cultures from dialysis catheter (by experienced staff), bloods. Urine culture, if appropriate; consider bladder US if pyocystis suspected. CXR, echo, and CT, as appropriate.
- *Further management*: line sepsis till proven otherwise. Antibiotics as per local guidelines, adjusted doses for dialysis patients. MRSA, *Staphylococcus aureus*, fungal-positive cultures: remove the dialysis line. Tunnel infections require line removal. Despite line removal, if

CRP remains elevated and unwell, consider a bacteraemic focus: echo, CT. Consider urological infection in those patients with old kidney transplants, polycystic kidneys, or urological abnormalities.

- *Caution administering IV fluids*, as will easily precipitate pulmonary oedema. If patients are hypotensive and underfilled, 250mL of normal saline may be administered, with regular assessment of the patient. Those patients unwell with sepsis and hypotension should be transferred to ITU for inotropic support.

Arteriovenous fistula infection

History and examination, as for fever in a haemodialysis patient and a tunneled haemodialysis line. Swab the arteriovenous fistula (AVF). Antibiotics are commenced, as per local microbiology guidelines. Surgical review. Consider imaging to assess for a collection.

Corticosteroids

Many patients will be administered long-term corticosteroids due to either: (1) previous transplantation or (2) their underlying disease which may have caused renal failure such as SLE and vasculitis. Those patients on long-term steroids are likely to require an increase in steroid dose. If unwell, this can be either IV hydrocortisone or an increase in oral prednisolone dose.

Peritoneal dialysis: transfer to local renal unit

Exit site infection

- Take swab of exit site. Send peritoneal fluid for cell count and culture.
- Antibiotics, as per local protocols for exit site infection.

Peritoneal dialysis peritonitis

This is characterized by cloudiness of the peritoneal dialysis fluid. If severe, patients may also have abdominal pain and, on examination, have signs consistent with peritonism.

- Antibiotics and duration of treatment, as per local protocols, are administered in the peritoneal dialysis fluid. This may consist of a gentamicin- or vancomycin-based regime, with monitoring of antibiotic levels.
- With MRSA, *S. aureus*, and fungal infections, consider peritoneal dialysis catheter removal. Removal may also be required for those patients with recurrent infection or failure to respond to treatment.

Guidelines

AKI

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Shock

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Sepsis syndrome and septic shock 336

Septic shock: management 338

Sepsis syndrome/septic shock: antibiotics 340

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Shock

Shock is defined as inadequate perfusion of vital organs. Concurrent hypotension need not necessarily be present. Unwell patients with a lactate $>2\text{mmol/L}$ may have inadequate perfusion. The drop in BP is a late finding, particularly in young, fit people, so resuscitation should ideally commence before this point is reached.

Priorities

- *If the BP is unrecordable, call the cardiac arrest team.* Begin basic life support with chest compressions; attach a defibrillator, and establish venous access.
- *If the BP (MAP $<60\text{mmHg}$) is low or falling, call for urgent support and/or specialist help, e.g. intensive care unit.*
- The cause of hypotension is often apparent. If it is not, then one can usually make a rapid clinical assessment of likely causes:
 - Hypovolaemia.
 - Cardiac failure.
 - Systemic vasodilatation, e.g. sepsis, anaphylaxis, neurogenic.
 - Obstruction (e.g. PE, tension pneumothorax, tamponade).
 - Combined causes.

Differential diagnosis of shock

Cardiac pump failure

- MI (➡ ST elevation myocardial infarction (STEMI), pp. 12–13).
- Dissection of the thoracic aorta (➡ Aortic dissection: assessment, pp. 148–9).
- Cardiac arrhythmias (➡ Arrhythmias: general approach, p. 58).
- Acute valvular failure or acute VSD (➡ Ventricular septal defect post-myocardial infarction (MI), pp. 34–5).
- Drug overdose (cardiac depressants; ➡ Overdoses: general approach, pp. 740–1).
- Myocarditis.

Hypovolaemia

- Haemorrhage (GIT) (➡ Acute upper gastrointestinal bleeding 1, pp. 228–9), aortic dissection or leaking AAA, trauma (fractures, liver or spleen injury, haemothorax, occult).
- Fluid losses (diarrhoea, vomiting, polyuria, or burns).
- ‘Third space’ fluid losses (acute pancreatitis; ➡ Acute pancreatitis: assessment, pp. 284–5).
- Adrenal failure (➡ Addisonian crisis: assessment, pp. 578–80).

Systemic vasodilatation

- Sepsis.
- Liver failure (➡ Acute liver failure: assessment and investigations, pp. 276–7).
- Drug overdose (calcium antagonists or other vasodilators, drugs causing multi-organ failure, e.g. paracetamol, paraquat).
- Adrenal failure (may be both hypovolaemic and vasodilated).
- Neurogenic shock (bradycardia and hypotension, autonomic failure).

Systemic vasodilatation: anaphylaxis

- Recent drug therapy.
- Food allergy (e.g. peanut).
- Insect stings.

Obstruction

- Cardiac tamponade (➡ Cardiac tamponade: presentation, pp. 162–3).
- PE (➡ Pulmonary embolism (PE): assessment, p. 126).
- Tension pneumothorax (➡ Tension pneumothorax, p. 216).

Shock: assessment

If the BP is unrecordable, then call the cardiac arrest team. Begin basic life support (Airway, Breathing, Circulation, Disability/neurology, Exposure/environment), with emphasis on good-quality CPR, and establish venous access. If the cause of hypotension is not obvious, perform a rapid clinical examination, looking specifically for the following:

- Check the airway is unobstructed. Give high-flow (60–100%) O₂ by face mask. If airway is unprotected or breathing inadequate, ETT. A laryngeal mask airway (LMA) can be used to help oxygenation but does not protect the airway like ETT. Check both lungs are ventilated (? tension pneumothorax).
- Note the respiratory rate (↑ in acidosis, pneumothorax, embolus, and cardiac failure, but often ↑ regardless of cause).
- Check cardiac rhythm, and treat if abnormal (➡ Tachyarrhythmias heart rate >120bpm, pp. 60–1; ➡ Treatment options in tachyarrhythmias, p. 62; ➡ Broad complex tachycardia: diagnosis, p. 64; ➡ Monomorphic ventricular tachycardia (MVT), pp. 66–7; ➡ Polymorphic ventricular tachycardia, pp. 68–9; ➡ Ventricular tachycardia: drugs, p. 70; ➡ Narrow complex tachyarrhythmias (SVT), pp. 72–3; ➡ Dosages of selected antiarrhythmics for SVT, p. 75; ➡ Atrial fibrillation: assessment, pp. 76–7; ➡ Atrial fibrillation: management, pp. 78–9; ➡ Atrial fibrillation: rate control, p. 81; ➡ Atrial flutter, p. 82; ➡ Multifocal atrial tachycardia, p. 83; ➡ Accessory pathway tachycardia (AV re-entrant tachycardia), p. 84; ➡ Atrioventricular nodal re-entry tachycardia, p. 85; ➡ Bradyarrhythmias: general approach, pp. 86–7; ➡ Sinus bradycardia or junctional rhythm, p. 88; ➡ Intraventricular conduction disturbances, p. 89; ➡ Types of atrioventricular conduction block, p. 90).
- Is the JVP elevated (see Box 5.1)?
- Is the BP the same in both arms (thoracic aortic dissection)?
- Are there any unusual cardiac murmurs? (Acute valvular lesion, flow murmurs, including an S3, are often heard in vasodilated patients.)
- Is the patient cold and clammy? This suggests cardiac failure or hypovolaemia. NB Patients with septic shock may also be peripherally shut down. Check for fever (temperature may be subnormal, especially in the elderly and children).
- Is the patient warm and systemically vasodilated (capillary refill time). Palpate for bounding pulses.
- Is the patient clinically dehydrated or hypovolaemic (skin turgor, mucous membranes, postural fall in BP)?
- Any evidence of haematemesis (blood around the mouth) or melaena [per rectum (PR) examination]?
- Is there any evidence of anaphylaxis, including urticaria, wheeze, or soft tissue swelling (e.g. eyelids or lips)?
- Examine the abdomen. Is there fullness or a pulsatile mass in the abdomen (ruptured aneurysm)? Is there evidence of an acute abdomen [aneurysm (mottled legs), pancreatitis, perforated viscus]?
- Is conscious level impaired [AVPU (Alert, Voice, Pain, Unresponsive), Glasgow Coma Scale (GCS)]?
- Is there evidence of trauma or fractures?

Investigations

ECG

- NSTEMI, STEMI, Q waves, arrhythmias, PE (tachycardia, right heart strain, S1, Q3, T3), pericarditis (global ST elevation with PR depression).

CXR

- Pneumothorax, PE (oligaemia), dissection (wide mediastinum), tamponade (globular cardiomegaly), pleural effusion (blunted costophrenic angles).

Blood tests

- FBC (haemorrhage, ↓ platelets in liver disease and sepsis), U&Es (renal impairment, adrenal failure), *glucose*, *coagulation screen* (liver disease, DIC), LFTs, troponin, CK, *group and screen/cross-match*.

ABGs

- Acidaemia, renal, lactate, ketoacidosis.

Septic screen

- Culture of blood, urine, sputum, and viral swabs.

Miscellaneous

- Echo (suspected tamponade, dissection, valve dysfunction), FAST scan, LP, USS, CT abdomen and head.

Box 5.1 Causes of hypotension with a raised CVP

- PE ➡ Pulmonary embolism (PE): assessment, p. 126.
- Cardiac tamponade (➡ Cardiac tamponade: presentation, pp. 162–3).
- Cardiogenic shock (➡ Cardiogenic shock, pp. 44–5).
- Fluid overload in shocked vasodilated patients.
- RV infarction (➡ Right ventricular infarction, p. 28).
- Tension pneumothorax (➡ Tension pneumothorax, p. 216).

Shock: management

General measures

- Check the airway patency; give O_2 (60–100%) by face mask to optimize O_2 saturation. If conscious level is impaired (GCS <8), or airway is compromised, or oxygenation is inadequate, consider airway adjuncts (nasopharyngeal, Guedel) and subsequent intubation (or supraglottic device, such as LMA, if ETT is not possible).
- Lie the patient flat; elevate the legs to improve venous return and demonstrate hypovolaemia.
- Insert two large-bore IV cannulae, and commence infusion of a crystalloid (Ringer's lactate/Hartmann's solution, Plasma-Lyte; 0.9% saline if hyperkalaemia or hypercalcaemia suspected). In most cases of shock, including cardiac causes, it is usually beneficial and safe to give a crystalloid (250mL boluses over 5–10min), while a more detailed assessment is being carried out. If the fluid challenge brings improvement, give a further fluid challenge while assessing the situation. If large volumes of crystalloid are needed, it is best to avoid exclusive use of 0.9% saline, which may cause hyperchloraemia and metabolic acidosis. Aim for 30mL/kg of crystalloid if septic shock.
- Send blood for U&Es, Mg^{2+} , bone profile, glucose, CRP, FBC, coagulation screen, X-match, blood cultures, and blood gas (venous and/or arterial).
- Insert an arterial line for more accurate assessment of the BP and arterial sampling. Catheterize the bladder to monitor the urine output. Metaraminol and ephedrine can be given through a peripheral line to temporarily improve the BP.
- Titrate fluid replacement according to appropriate available dynamic parameters: stroke volume (variation <10%), central venous SpO_2 (>75mmHg), venous–arterial CO_2 gap (≤ 0.5 mmHg), HR, BP, peripheral tissue perfusion, and urine output (>0.5mL/kg/h). Overenthusiastic fluid administration in patients with cardiac pump failure will precipitate pulmonary oedema.
- Persistent hypotension, despite adequate filling, is an indication for inotropic support, assuming that tension pneumothorax and PE have been excluded. Insert a central venous line for inotrope infusions. The choice of first-line agent varies to some extent, depending upon the underlying diagnosis, but NA is a reasonable choice supported by RCTs.
- Treat the underlying condition, and *enlist specialist help early*.
- Ensure someone takes time to talk to the relatives to explain the patient is seriously ill and may die. Discuss the resuscitation status.

See Box 5.2.

Cardiogenic shock (cardiac pump failure)

- Manage cardiac ischaemia, arrhythmias, and electrolyte disturbances.
- Possible concurrent hypovolaemia? Consider cautious IV fluid challenges, rather than infusions. Optimize filling, guided by physical signs and response in filling pressures and stroke volume to fluid challenges (100–250mL of crystalloid).

- If BP allows (aim for SBP >100mmHg), start a nitrate infusion (e.g. GTN 1–10mg/h).
- If very hypotensive, start an IV inotrope infusion. NA should be commenced. The addition of levosimendan or dobutamine should be considered, as per local protocols.
- Milrinone and/or sildenafil may help in the presence of severe pulmonary hypertension, but expert assistance is advised.
- Low-dose diamorphine (e.g. 2.5mg) is beneficial, as it vasodilates, reduces anxiety, and lowers the metabolic rate.
- Consider non-invasive (CPAP) or invasive ventilation in patients with severe heart failure, as this decreases the work of breathing and benefits both LV afterload and preload.
- If there is a potentially reversible cause for cardiogenic shock, consider intra-aortic balloon counterpulsation with heparin anticoagulation as an option, but this does not improve survival in RCTs (➡ Intra-aortic balloon counterpulsation 1, p. 822).
- TTE would be helpful in assessing cardiac function and response to fluid and vasopressors.

Hypovolaemic shock

- Fluid replacement with crystalloids; colloids do not offer a survival advantage but achieve a more rapid haemodynamic response.
- Give blood to maintain Hb 70–90g/L; 90–100g/L in ACS or sepsis.
- Na⁺ and K⁺ abnormalities should be treated. Metabolic acidosis often responds to fluid replacement alone.
- If the patient remains hypotensive in spite of fluids, consider other causes of shock (sepsis, tamponade, tension pneumothorax, etc.). Reperfusion injury may occasionally manifest itself as a hypotensive and vasodilated circulation. If fluid-replete, commence inotropes–NA, perhaps with the addition of levosimendan or dobutamine if a low cardiac output state is suspected.
- If oliguria persists in an overloaded, resuscitated patient, furosemide (0.5–1.0mg/kg IV bolus, followed by an infusion of 1–10mg/h IV) may be given to try and maintain a urine output, as this may make fluid management easier. There is no evidence that furosemide improves outcome.

Box 5.2 Management key points: shock

- ABC, O₂ (60–100%); consider intubation if GCS <8.
- IV access and fluids: titrate according to BP, CVP, and urine output. (In most cases, it is safe to give 250mL of crystalloid over 5–10min and assess response.)
- Inotropes: if there is persistent hypotension in spite of adequate filling.
- After initiating inotropes, assess the patient frequently for tachyphylaxis (may require dose titration) and additional haemodynamic insults.
- Treat the underlying condition, e.g. infections, cardiac ischaemia, or arrhythmia.
- Talk to the relatives. Discuss the resuscitation status.

Practice points

Survival advantage is not gained with saline, compared to albumin,¹ gelatin,² or starch,³ for fluid resuscitation for sepsis.

References

1. Patel A, Laffan MA, Waheed U, Brett SJ. Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. *BMJ* 2014;**349**:g4561.
2. Patel A, Brett SJ. Gelatin solutions for critically unwell septic adults. *Br J Hosp Med (Lond)* 2013;**74**:657.
3. Patel A, Waheed U, Brett SJ. Randomised trials of 6 % tetrastarch (hydroxyethyl starch 130/0.4 or 0.42) for severe sepsis reporting mortality: systematic review and meta-analysis. *Intensive Care Med* 2013;**39**:811–22.

Sepsis syndrome and septic shock

Definitions

- *Bacteraemia* Positive blood cultures.
- *Systemic inflammatory response syndrome (SIRS)* SIRS not thought to be due to infection. Two or more of: temperature $>38.3^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, RR 20/min or $P_a\text{CO}_2 <32\text{mmHg}$ (4.3kPa), HR 90bpm, total WCC $>12 \times 10^9/\text{L}$ or <4 .
- *Sepsis* Evidence of infection plus systemic inflammatory response.
- *Severe sepsis* Sepsis plus evidence of organ dysfunction: confusion, hypoxia, oliguria, metabolic acidosis.
- *Septic shock* Severe sepsis with hypotension refractory despite adequate fluid resuscitation, or lactic acidosis (lactate $>4\text{mmol/L}$).

NB These definitions are in the process of being redefined, with an emphasis on criteria being present in critically unwell patients.

Presentation

General symptoms

Sweats, chills, or rigors. Breathlessness. Headache. Confusion in 10–30% of patients, especially the elderly. Nausea, vomiting, or diarrhoea may occur.

Examination

Hypotension (SBP $<90\text{mmHg}$ or a 40mmHg fall from baseline) and tachycardia, with peripheral vasodilatation (warm peripheries, bounding peripheral pulse, bounding pulses in forearm muscles) are the hallmarks of early sepsis, but patients do become shut down eventually. SVR is reduced and cardiac output is $\uparrow$ initially, but severe myocardial depression may occur. Other features include fever $>38^{\circ}\text{C}$ or hypothermia $<35.6^{\circ}\text{C}$ (immunocompromised or elderly patients may not be able to mount a febrile response), tachypnoea and hypoxia, metabolic acidosis, and oliguria. Focal physical signs may help to localize the site of infection.

Investigations

- *Blood tests* Blood cultures, U&Es, blood sugar, FBC, coagulation studies, LFTs, CRP, group and save, serum lactate, ABGs. Amylase, CK, and serology. Procalcitonin which is more specific for bacterial sepsis.
- *Culture* Blood, sputum, urine, lines and tips, wound swabs, throat swab, drain fluid, stool, nasopharyngeal aspirate for viral PCR, MRSA swabs, CSF (as indicated), blood films (if recent travel).
- *Imaging* CXR, USS, or CT brain, chest, abdomen, and pelvis for collections. Echo if endocarditis suspected.

Continuous assessments in ICU/HDU

Patients should be monitored in either an ICU or HDU. An arterial line should be inserted for continuous BP monitoring and intermittent blood sampling. It is important in the management of such critically ill patients *not* to lose sight of the needs of the patient. It is easy in an ICU setting not to

examine patients but to look at charts. Always examine the patient at least twice a day and determine whether the clinical parameters match those on the ICU chart.

Ask yourself twice a day

- Is gas exchange satisfactory? Watch for developing ARDS (➡ Adult respiratory distress syndrome 1, p. 204) or ventilator-associated pneumonia. Examine the chest daily for deterioration that may be masked on ABG by adjustments of mechanical ventilation and do a CXR if needed.
- Is the circulation adequate? Note the BP (and MAP), filling pressures, and cardiac output. Examine the peripheries (are they cool and shut down, or warm?). Is the urine output satisfactory? Is there a swing on the arterial trace, suggestive of hypovolaemia? Is there a developing metabolic acidosis, or rising lactate, which may indicate tissue hypoperfusion?
- Fluid requirements. (What is the fluid balance? Is the patient clinically dry, euvolaemic, or oedematous?)
- Is the patient receiving adequate nutrition (TPN or enteral)? Give enteral nutrition, if possible; even 10mL/h will benefit the gut mucosa. Give with TPN if the gut function is not adequate, but ensure regular aspiration of any unabsorbed feed.
- What do the tests show [U&Es, LFTs, Ca^{2+} , PO_4^{3-} , Mg^{2+} , CRP, cultures (blood, urine, sputum, lines and tips, etc.)?]
- Are there signs of sepsis? Is there a new focus of infection?

Prognosis

The incidence of bacteraemia is 7/1000 admissions to hospital. Of these, 20% develop septic shock and ~50% of these die (see Table 5.1; also see Box 5.3).

Table 5.1 Mortality in sepsis

	Mortality (%)
Bacteraemia	15–30
Bacteraemia plus septic shock	30–50
Septic shock plus ARDS	50–70

Box 5.3 Poor prognostic features in sepsis syndrome

- Age >60.
- Multi-organ failure (>3 organs).
- Renal failure.
- Respiratory failure (ARDS).
- Hepatic failure.
- Hypothermia.
- Leucopenia or neutropenia.
- Hospital-acquired infection.
- DIC.
- Thrombocytopenia.
- Underlying disease (e.g. immunocompromised, poor nutritional status, malignancy).

Septic shock: management

Patients with established shock require adequate haemodynamic monitoring and high-dependency facilities.

Check the airway is clear. Give high-flow O_2 —if there is refractory hypoxia, intubate and ventilate. Insert a large-bore peripheral venous cannula to begin fluid resuscitation. Insert a central line and an arterial line.

Key recommendations from the updated Surviving Sepsis Campaign guidelines (2012)⁴ for management of severe sepsis and septic shock are summarized here:

- *Early goal-directed resuscitation*: during the first 6h after recognition (in patients with hypotension or serum lactate $>4\text{mmol/L}$) is current practice but not supported by multiple RCTs.
- *Resuscitation goals include*:
 - MAP $\geq 65\text{mmHg}$.
 - Central venous O_2 saturation $\geq 70\%$.
 - Urine output $\geq 0.5\text{mL/kg/h}$.
- *Source identification*:
 - Within first 6h of presentation.
 - Blood cultures before antibiotic therapy.
 - Culture all sites as clinically indicated.
 - Imaging studies performed promptly to confirm potential source of infection.
- *Broad-spectrum antibiotics*:
 - Within 1h of diagnosis of severe sepsis/septic shock (give first dose of antibiotics yourself).
 - Daily reassessment of antimicrobial therapy with microbiology and clinical data.
 - Antibiotic therapy guided by clinical response; normally 7–10 days, but longer if response is slow or if there are undrainable foci of infection or immunologic deficiencies.
- *Source control*: abscess drainage, tissue debridement, or removal of IV access devices if potentially infected as soon as possible, following successful initial resuscitation (exception: infected pancreatic necrosis where surgical intervention is best delayed).
- *IV fluids*:
 - Crystalloid fluid challenge (e.g. 1L of crystalloids over 30min) to restore circulating volume; aim for 30mL/kg.
 - Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent haemodynamic improvement.
- *Vasopressors*:
 - NA or dobutamine (administered centrally) are first line.
 - Vasopressin infusion (or long-acting terlipressin bolus) may be added to NA.
- *Inotropic therapy*: consider dobutamine when cardiac output remains low, despite fluid resuscitation and vasopressor therapy.
- *Steroids*: hydrocortisone (50mg 6-hourly), after adequate fluid resuscitation, may be considered in refractory shock but does not improve survival.

- *Blood products:*
 - Target Hb of 70–90g/dL. Aim for a higher target in the presence of tissue hypoperfusion, CAD, intracerebral pathology, or acute haemorrhage.
 - Do not use FFP to correct laboratory clotting abnormalities, unless there is bleeding or planned invasive procedures.
 - Administer platelets when platelet counts are $<20 \times 10^9/L$ and there is significant bleeding risk.
 - Liaise closely with haematology, especially if DIC is suspected.
- *Ventilation:*
 - A strategy of low tidal volume, driving pressure, and inspiratory plateau pressure to prevent ARDS.
 - Positive end-expiratory pressure (PEEP).
 - Head of bed elevation in mechanically ventilated patients, unless contraindicated.
- *Glucose control:* use IV insulin to control hyperglycaemia, targeting a blood glucose $<10\text{mmol/L}$ after initial stabilization.
- *Renal replacement:* continuous haemofiltration is the preferred method.
- *DVT prophylaxis:* low-dose UFH (renal impairment) or LMWH, unless contraindicated, with dynamic compression (e.g. Flowtron®) of the legs, unless contraindicated.
- *Stress ulcer prophylaxis:* H_2 blockers or PPIs.
- *Consideration of limitation of support* (where appropriate): discuss advance care planning with patients and families. Describe likely outcomes and set realistic expectations.

References

4. Dellinger RP, Levy MM, Rhodes A, et al. (2012). Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. *Intensive Care Med* 39:165–228.

Sepsis syndrome/septic shock: antibiotics

Antibiotic choice is dictated by the suspected site of infection, probable organism, host factors (e.g. age, immunosuppression, hospitalization, and local antibiotic resistance patterns), and local sensitivities. A suggested empiric regimen is presented by source of sepsis:

- *Pneumonia—community-acquired*: co-amoxiclav + clarithromycin or azithromycin or doxycycline.
- *Pneumonia—hospital-acquired*: piperacillin and tazobactam + gentamicin or amikacin. NB If *Staphylococcus aureus* suspected, add teicoplanin or vancomycin (if MRSA) or flucloxacillin (if MSSA).
- *Intra-abdominal sepsis*: piperacillin and tazobactam + metronidazole + gentamicin or amikacin.
- *Biliary tract*: piperacillin and tazobactam + gentamicin or amikacin.
- *Urinary tract—community-acquired*: co-amoxiclav or ciprofloxacin or fosfomycin.
- *Urinary tract—hospital-acquired*: piperacillin and tazobactam or gentamicin or amikacin or ciprofloxacin.
- *Skin and soft tissue*: co-amoxiclav + flucloxacillin and clindamycin.
- *Sore throat*: benzylpenicillin.
- *Multiple organisms (anaerobes, Escherichia coli, Streptococcus)*: meropenem + vancomycin or teicoplanin + gentamicin or amikacin + metronidazole.
- *Meningitis*: ceftriaxone and amoxicillin or (if pen. and cef. allergic) vancomycin or rifampicin or chloramphenicol.

NB Consult your microbiologists for local antibiotic policy.

Remove infective foci

It is essential to identify and drain focal sites, e.g. obstructed urinary tract or biliary tree, drain abscesses, and to resect dead tissue.

Causes of treatment failure

- Resistant or unusual infecting organism.
- Undrained abscess/ongoing source of sepsis.
- Inflammatory response (raised CRP, raised WCC) may persist, despite adequate antimicrobial therapy.
- Advanced disease.
- Ongoing immunosuppression/neutropenia.
- Incorrect diagnosis.

Toxic shock syndrome

- Distinct clinical illness caused by toxin-producing Gram-positive bacteria, usually staphylococci or streptococci.
- Infection is often localized, and illness is manifest by toxins (e.g. superantigens).
- 85% of cases are ♀.
- Association with use of tampons and postpartum in ♀ or following nasal packing (either sex).
- May occur with any focal infections due to a toxin-producing strain, including post-operative wound infections.

Clinical features

- Fever: $>38.9^{\circ}\text{C}$.
- Rash: diffuse macular (seen in $\geq 95\%$), mucous membrane involvement common. Desquamation 1–2 weeks later, palms and soles (non-specific: consider drug reaction in differential diagnosis).
- Hypotension: SBP $<90\text{mmHg}$, or postural hypotension; often fluid-unresponsive.
- Diarrhoea and vomiting are common.
- NSAIDs may mask symptoms.
- DIC and petechial rash.
- Multi-organ failure may rapidly follow.

Laboratory findings

- Normochromic normocytic anaemia (50%) and leucocytosis ($>80\%$).
- Renal/hepatic failure (20–30%).
- Myalgia and elevated CK are common.
- DIC.
- Pyuria.
- CSF pleiocytosis (sterile).
- Blood cultures rarely positive.
- Vaginal swabs, throat swab, and wound swabs.
- Toxin-producing *S. aureus* in 98% of menses-associated cases.
- Sometimes positive ASO titres or anti-staphylococcal antibodies.

Therapy

- Limit toxin production/release.
- Drain any focal collections and remove foreign bodies.
- Anti-staphylococcal antibiotics (high-dose flucloxacillin, teicoplanin, or clindamycin IV).
- Supportive care, as for any patient with shock.

Anaphylaxis

Anaphylaxis is a severe, life-threatening generalized or systemic hypersensitivity reaction, characterized by rapidly developing life-threatening airway and/or breathing and/or circulation problems, usually associated with skin and mucosal changes. The UK incidence of anaphylactic reactions is increasing.

Atopic individuals are particularly at risk, but it may occur in the absence of a past history. Urticarial disease may also present with anaphylaxis. Precipitants include:

- Insect bites (especially wasp and bee stings).
- Foods and food additives (e.g. peanuts, fish, eggs).
- Drugs and IV infusions (blood products and IV immunoglobulin, vaccines, antibiotics, aspirin and other NSAIDs, iron injections, heparin, monoclonal antibodies, e.g. rituximab).

Presentation

Cutaneous features include skin redness, pruritus, urticaria, conjunctival injection, angio-oedema, and rhinitis. More severe manifestations include laryngeal obstruction (choking sensation, cough, stridor), bronchospasm, tachycardia, hypotension, and shock.

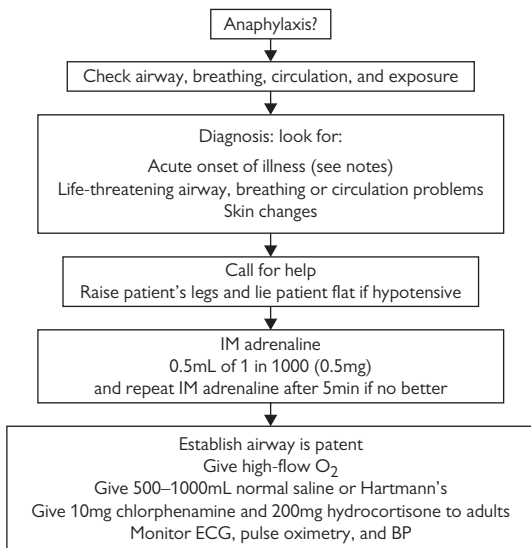
Management

(See Fig. 5.1.)

- Remove the suspected precipitant if still being received.
- *Maintain the airway*: if respiratory obstruction is imminent, intubate and ventilate. Consider emergency cricothyroidotomy (➡ Percutaneous cricothyrotomy, p. 832) with a 14G needle and jet insufflation with 100% O₂ if intubation not possible.
- Give 100% O₂: if there is refractory hypoxaemia, intubate and ventilate.
- Lie the patient flat with head-down tilt if hypotensive/legs raised.
- Give IM adrenaline 0.5–1mg (0.5–1mL of 1 in 1000 adrenaline injection), and repeat every 10min according to BP and pulse.
- If IV access is present, use small IV doses of adrenaline (0.1–0.2mg), then review response. SC adrenaline should not be given in anaphylactic shock due to variable absorption.
- Establish venous access, and start IV crystalloid fluids (e.g. 500mL over 30min). Persistent hypotension requires a continuous adrenaline infusion, titrated to BP response.
- Give IV hydrocortisone 200mg and chlorphenamine 10mg.
- Continue H₁ antagonist (e.g. chlorphenamine 4mg every 4–6h) for at least 24–48h longer if urticaria and pruritus persist.
- If bronchospasm does not subside, treat as severe asthma (including salbutamol, nebulized or intratracheal adrenaline, aminophylline).
- Once stable, consider investigations such as timed trypase levels, IgE level, complement.

Angioneurotic oedema (C₁ esterase inhibitor deficiency)

See ➡ C₁ esterase inhibitor deficiency (angioneurotic oedema), p. 689.

**Acute onset of illness:**

- *Airway*: swelling, hoarse voice, stridor
- *Breathing*: wheeze, shortness of breath, respiratory arrest
- *Circulation*: pale, clammy, tachycardia, shock, cardiac arrest.

Skin changes may be subtle or dramatic, involving both skin or mucosae. There may be erythema, or there may be urticaria which can appear anywhere on the body. The weals are usually itchy and may be pale, pink or red, or look like nettle stings. They can be different shapes and sizes, and are often surrounded by a red flare.

Fig. 5.1 Treatment algorithm for anaphylaxis.

Lactic acidosis

Lactic acidosis is a metabolic acidosis due to excess production, or reduced metabolism, of lactic acid. It may be divided into two types: *type A* (tissue hypoperfusion) and *type B* (non-hypoxic).

Presentation

Patients are usually critically ill. Clinical features include:

- Shock (often BP <80/40mmHg).
- Kussmaul respiration.
- Tachypnoea.
- Deteriorating conscious level.
- Multi-organ failure, including hepatic, cardiac, and renal failure.
- Clinical signs of poor tissue perfusion (cold, cyanotic peripheries).

Investigations

- ABGs (pH <7.34, severe if pH <7.2).
- Serum electrolytes, including bicarbonate and chloride to calculate the anion gap, if lactate unavailable. Raised anion gap >16mmol/L [anion gap = $(\text{Na}^+ + \text{K}^+) - (\text{bicarbonate} + \text{chloride})$].
- FBC (anaemia, neutrophilia).
- Blood glucose.
- Blood lactate level >4mmol/L (mainly done on ABG analysers).
- Screen for sepsis (blood cultures, CRP, MSU, etc.).
- Spot urine (50mL) for drug screen if cause unknown.
- CXR looking for consolidation or signs of ARDS.

Assessment of severity

Severity is assessed by blood lactate concentration and the degree of acidaemia. This may be confounded by the presence of AKI. In the early stages, the arterial pH may be normal or even raised, as elevated lactate levels in the CNS cause hyperventilation, with compensatory respiratory alkalosis. The best predictor of survival is the arterial pH. Patients presenting with a lactate of >5mmol/L and a pH <7.35 have a mortality of >50%.

Management

The principle of management is diagnosis and treatment of the cause (see Box 5.4). All patients should be managed in a high-dependency area.

- *Sepsis*: start broad-spectrum antibiotics (e.g. cefotaxime + metronidazole).
- *Diabetic lactic acidosis*: insulin and fluids, as needed (➡ Diabetic ketoacidosis: assessment, pp. 546–7).
- *Shock*: consider invasive haemodynamic monitoring (➡ Shock: management, pp. 332–3).
- *Renal failure*: treat by continuous haemo(dia)filtration. These patients are usually too unstable to tolerate haemodialysis.
- *Methanol*: infuse ethanol or fomepizole (competitive metabolism; ➡ Toxic alcohols, pp. 780–1).
- *Acidaemia*: the role of bicarbonate is controversial, as it may lower CSF pH. There is no benefit of bicarbonate over equimolar saline in controlled trials.

Box 5.4 Causes of lactic acidosis**Type A: tissue hypoperfusion**

- Septic shock (tissue hypoperfusion).
- Shock.
- Severe anaemia.
- Severe hypoxia.
- Catecholamine excess (e.g. phaeochromocytoma or exogenous).
- Severe exercise.

Type B: abnormal metabolism

- Sepsis (mitochondrial impairment).
- Renal failure.
- Hepatic failure.
- DM (uncontrolled).
- Malignancy (leukaemia, lymphoma).
- Acute pancreatitis.
- Thiamine deficiency.

Drug-induced

Paracetamol (acetaminophen) overdose, metformin, methanol, ethanol, salicylates, ethylene glycol, and cyanide.

Rare causes

Hereditary enzyme defects such as glucose-6-phosphatase and fructose-1,6-diphosphatase deficiency.

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Coma: assessment

Presentation

Coma is a 'state of *unarousable unresponsiveness*'.

- *No evidence of arousal*: there is no spontaneous eye opening, comprehensible speech, or voluntary limb movement.
- *Unresponsive* to external stimuli and surrounding environment, although abnormal postures may be adopted, eyes may open, or grunts may be elicited in response to pain.
- *Involuntary movements*, e.g. seizures or myoclonic jerks, may occur.
- GCS (➡ Glasgow Coma Scale (GCS), p. 458) is a useful way of assessing and monitoring level of consciousness.
- *Signs of brain shift* (➡ Examination of brainstem function 3, pp. 464–5) may accompany a decreasing level of consciousness.

Causes

For practical purposes, it is best to divide these into:

- Metabolic.
- Toxic.
- Infective.
- Structural lesions.

With or without:

- Focal brainstem signs.
- Lateralizing cerebral signs.
- Meningeal irritation.

In general, toxic and metabolic causes usually do not produce focal signs (except rarely with hypoglycaemia or liver or renal failure), whereas infections and structural lesions do. Meningism offers a very useful clue about the cause of coma (see ➡ Coma with meningism, p. 349).

Coma without focal/lateralizing neurological signs

- Anoxia/hypoperfusion.
- Metabolic, e.g. hypo-/hyperglycaemia, acidosis/alkalosis, hypo- or hypernatraemia, hypercalcaemia, hepatic or renal failure.
- Intoxications, e.g. alcohol, opiates, benzodiazepines, tricyclics, neuroleptics, lithium, barbiturates, carbon monoxide.
- Endocrine: hypothyroidism.
- Hypo- or hyperthermia.
- Epilepsy.
- Hypertensive encephalopathy.

Coma with focal/lateralizing neurological signs (due to brainstem or bihemispheric cerebral dysfunction)

- Vascular: cerebral haemorrhage or infarction (e.g. large-territory infarct or basilar artery thrombosis).
- Supra- or infratentorial space-occupying lesion (SOL): tumour, haematoma, abscess. In order to produce coma, these either have to be within the brainstem or compress it by producing a brain shift (➡ Examination of brainstem function 3, pp. 464–5).

Coma with meningism

- Meningitis, encephalitis.
- SAH.

Assessment of severity

- GCS (➡ Glasgow Coma Scale (GCS), p. 458).
- Signs of brain shift (➡ Examination of brainstem function 3, pp. 464–5) and/or brainstem compromise.
- Precipitating lesion or injury.
- Length of time in comatose state.
- Comorbidities.

Coma: immediate management

Priorities

1. Stabilize the patient (airway, breathing, circulation). Give O₂.
2. Consider giving thiamine, glucose, naloxone, or flumazenil.
3. Examine the patient. Is there meningism? Establish the GCS score. Is there evidence of brainstem failure? Are there focal or lateralizing signs?
4. Plan for further investigations.
5. Observe for signs of deterioration, and attempt to reverse them.

For treatments to be considered in coma, see Box 6.1.

Stabilize the patient

- *Open the airway* by laying the patient on their side. Note the pattern of breathing (➡ Examination of brainstem function 2, p. 462). If there is apnoea or laboured or disturbed breathing, intubation and ventilation should be considered. Measure ABGs.
- *Support the circulation*. Correct hypotension with fluids and/or inotropes. If prolonged therapy is required, both require careful and frequent monitoring of CVP and/or pulmonary artery wedge pressure (PAWP). Search for any occult source of bleeding, e.g. intra-abdominal.
- *Treat seizures* with usual drugs (➡ Status epilepticus (tonic-clonic) 1, pp. 408–9), but beware of over-sedation and hypotension.
- Take blood for *glucose, U&Es, Ca²⁺, liver enzymes, albumin, clotting screen, FBC*, and *toxicology* (including urgent paracetamol and salicylate levels). Urine should be saved for *toxicology screen*.

Give thiamine, glucose, naloxone, or flumazenil

- Check blood glucose. There is a good argument for giving 50mL of 50% glucose immediately for presumed hypoglycaemia because this will usually not cause any harm.
- The only concern is that glucose may precipitate Wernicke's encephalopathy (WE) in malnourished individuals. Some clinicians therefore favour giving a bolus of *thiamine* 100–200mg IV beforehand.
- *Naloxone* should only be given if opiate intoxication is likely (small pupils) and the patient is in a coma or has a markedly reduced RR. In adults, naloxone 0.8–2.0mg IV should be given at intervals of 2–3min to a maximum of 10mg.
- *Flumazenil* should only be administered if benzodiazepine intoxication is likely; it is contraindicated in epileptics who have received prolonged benzodiazepine therapy. In adults, flumazenil 200 micrograms should be given over 15s; further 100-microgram boluses may be given at 1-min intervals (usual dose is 300–600 micrograms, maximum total dose outside intensive care setting is 1mg).
- Both naloxone and flumazenil may be given as IVs if drowsiness recurs, but intensive care monitoring is advisable.

Box 6.1 Key points: treatments to be considered in coma

- Resuscitate (ABC, O₂).
- IV fluids to correct hypotension (and inotropes if necessary).
- Glucose (50mL of 50%) for hypoglycaemia.
- Thiamine 100–200mg IV in malnourished/alcoholic individuals before glucose (to avoid precipitating WE).
- Naloxone: if opiate intoxication is likely (small pupils or reduced RR). In adults, 0.4–2.0mg IV may be given at intervals of 2–3min to a maximum of 10mg.
- Flumazenil: if benzodiazepine intoxication is likely. In adults: 200 micrograms over 15s; further 100-microgram boluses may be given at 1-min intervals (maximum total dose outside ITU is 1mg).
- Therapeutic hypothermia to temperatures between 32°C and 34°C after cardiac arrest.

Coma: clues from examination

History

If available, this will often be the most useful source of assessment. Even if the history is not extensive, a witness is vital to establish whether coma commenced suddenly (suggestive of a vascular event) or whether there was a gradual decline in level of consciousness over hours or days and for relevant premorbid history (e.g. previous generalized seizures, use of drugs, etc.). Individuals known to suffer from specific diseases may be wearing a MedicAlert bracelet or carrying their regular medication. An enormous amount may be learnt from a rapid, but thorough, examination.

General examination

This should establish the following:^{1,2}

- *Core temperature*: fever usually indicates an infection but sometimes results from diencephalic lesions. Hypothermia is often forgotten as a cause for coma; the possibility of myxoedema should be considered. Ideally, prognosis should be based on normothermic state.
- *HR and rhythm*: may indicate a dysrhythmia as the reason for poor cerebral perfusion.
- *BP*: prolonged hypotension of any cause will lead to anoxia and ischaemia. Apart from a cardiac cause, occult bleeding, a cause of sepsis, and drug intoxication need to be considered.
- *Respiratory pattern*: shallow, slow breathing should alert the examiner to the possibility of drug intoxication, e.g. opiates. Deep, rapid Kussmaul breathing suggests acidosis. Brainstem compromise can cause distinctive patterns of breathing (see Fig. 6.4).
- *Breath*: alcohol, ketones, hepatic or uraemic fetor?
- *Skin*: there may be signs of trauma to the head. Bruising over the scalp or mastoids and blood in the nostrils or external auditory meatus raise the possibility of a basal skull fracture. A rash suggests the possibility of meningitis. Look for signs of chronic liver disease or sallow discoloration of uraemia. IV drug abuse suggested by needle tracks.
- *Heart*: occasionally bacterial endocarditis or vasculitides associated with heart murmurs present with coma.
- *Abdomen*: look for enlargement of organs which may give clues to the cause of coma. It is important not to miss an acute intra-abdominal event such as perforation of a viscus or a leaking aortic aneurysm.
- *Fundi*: papilloedema indicates raised ICP, but its absence does not exclude that possibility. Subhyaloid haemorrhages are pathognomonic of SAH but are rare. Changes of diabetic or hypertensive retinopathy suggest the possibility of encephalopathy secondary to these conditions.

Is there meningism?

Neck stiffness should be assessed only if it is certain that there has been no trauma to the cervical spine. Stiffness suggests meningeal irritation, either because of inflammation or infiltrative processes affecting the meninges or because of the presence of blood. Meningism raises the possibility of meningitis, meningococcal meningitis, or SAH. Start antibiotics immediately if meningitis is suspected.

Assess the GCS

This may reveal brainstem dysfunction or lateralizing signs. When testing the motor response, decorticate or decerebrate posturing may become evident (➡ Examination of brainstem function 1, pp. 460–1). If there is a change in these signs, it may indicate a brain shift (➡ Examination of brainstem function 3, pp. 464–5).

Look for evidence of brainstem dysfunction

See ➡ Examination of brainstem function 1, pp. 460–1 for details.

- Test and observe:
 - Pupillary response.
 - Corneal reflex.
 - Resting position of the eyes.
 - Spontaneous eye movements.
 - Oculocephalic response/doll's head manoeuvre (if no C-spine injury).
 - Oculovestibular response/caloric stimulation.
 - Swallowing.
 - If intubated: cough and gag to suction.
 - Respiratory pattern.
 - If intubated: ventilator dependency.
- There will be evidence of brainstem failure either because there is structural damage (intrinsic lesion or extrinsic compression due to brain shift; see ➡ Examination of brainstem function 3, pp. 464–5) or because of metabolic coma such as drug intoxication with diffuse, usually reversible, dysfunction.
- If there is focal brainstem dysfunction, the cause is most likely structural or intrinsic brainstem disease.
- If there is rostro-caudal progression of brainstem signs, consider a herniation syndrome (➡ Examination of brainstem function 3, pp. 464–5).
- If there appears to be diffuse brainstem dysfunction, it may not be easy to distinguish between structural and metabolic aetiologies. The most important clue is that in metabolic coma, irrespective of their size, the pupils continue to react, except in very few exceptional cases (atropine, hyoscine, or glutethimide intoxication will depress brainstem function and produce pupillary abnormalities).

Are there lateralizing signs?

Testing of brainstem reflexes, assessing the GCS score, and general examination may reveal facial asymmetry and differences in muscle tone, clonus, reflexes, and plantar responses between the two sides. All these features point towards the possibility of a structural lesion, although occasionally metabolic coma is associated with focal neurological signs.

References

1. Posner JB, Saper CB, Schiff ND, Plum F (2007). *Plum and Posner's Diagnosis of Stupor and Coma* (Contemporary Neurology Series), 4th edn. Oxford University Press, New York, NY.
2. Bates D. The management of medical coma. *J Neurol Neurosurg Psychiatr.* 1993;56:589–98.

Coma: management

Plan for further investigations

The history, physical examination, and/or laboratory studies may help make the diagnosis. Often, however, a diagnosis cannot be reached so rapidly. The practical approach is to divide patients according to the following scheme.

Brainstem function intact

Urgent CT head scan. This will reveal one of the following:

- Operable lesions (e.g. subdural, subarachnoid, or intracerebral haemorrhage): refer to neurosurgery as appropriate.
- Inoperable lesions: treatment is supportive.
- Normal CT: an LP should be performed. Measure the opening pressure. CSF analysis may suggest an infective process (e.g. meningitis, encephalitis) (➡ Acute bacterial meningitis: assessment, p. 371). If the CSF is normal, the most likely diagnosis is a metabolic coma.

Brainstem function not intact

- Consider whether there are signs of brain shift (➡ Examination of brainstem function 3, pp. 464–5).
- If a herniation syndrome appears to be progressing rapidly, mannitol should be given, hyperventilation commenced, and a neurosurgeon contacted urgently (➡ Raised intracranial pressure, pp. 388–90).
- If the tempo of events is not so rapid, mannitol may be given and an urgent CT scan arranged.
- Even if the brainstem signs appear to be non-progressive, a CT scan should be arranged to exclude the possibility of an operable posterior fossa mass or haemorrhage (e.g. cerebellar haemorrhage).
- If the CT is normal, an LP should be performed to exclude infection. If this too is normal, the diagnostic possibilities are intrinsic brainstem disease not detected by CT, metabolic coma, paraneoplasia, and parainfectious or possibly infection, e.g. encephalitis, without leucocytic response.
- MRI is more sensitive in detecting intrinsic brainstem pathology, but fluid attenuation inversion recovery (FLAIR) sequences are limited in sensitivity in this part of the brain. Additionally, standard 5-mm slices may be too thick for some discrete pathologies.
- LP should be repeated the next day if there is no improvement in the patient's condition. Treatment is supportive.

Monitoring progress

- Regular observations of vital signs and neurological state (and GCS score).
- An important cause of deterioration in structural brain lesions is brain shift leading to herniation syndromes (➡ Examination of brainstem function 3, pp. 464–5). The emergency treatment of raised ICP is discussed under ➡ Raised ICP: further management, p. 392.
- Other reasons for deterioration are electrolyte or metabolic changes, hypovolaemia, or fluid overload. Monitor regularly.

Prognosis

In coma due to head injury, prognosis is clearly related to the GCS score. Patients scoring 8 or less have a poor prognosis. In non-traumatic coma, the GCS score alone is not a very good predictor. Patients with drug intoxications may have low scores on admission but, in general, have good outcomes. Prognosis in non-traumatic coma is gauged by simple features of the examination. (e.g. if after 24h, pupillary responses, corneal reflexes, and oculovestibular response remain absent, survival is extremely unlikely).³ Early myoclonus (within 24h) after hypoxic–ischemic brain injury is a poor prognostic marker. Prognosis requires assessment at least 3 days subsequent to rewarming (if therapeutically cooled or patient presented in hypothermic coma).

References

3. Levy DE, Bates D, Caronna JJ, et al. Prognosis in nontraumatic coma. *Arch Int Med*. 1981;94: 293–301.

Limb weakness: assessment

History

The history should establish if there has been:

- Sudden onset or gradual progression.
- Weakness or incoordination.
- Upper limb or facial weakness.
- Asymmetrical or symmetrical weakness.
- Associated sensory symptoms, e.g. paraesthesiae or numbness.
- Difficulty with swallowing, speech, micturition, or defecation.
- Back or neck pain.
- Lhermitte's phenomenon (flexion of the neck causing sensory symptoms radiating down the limbs) suggests cervical cord inflammation, radiation-induced myelopathy, or vitamin B₁₂-deficient subacute degeneration of the cord.
- Systemic symptoms, e.g. malaise, fever, diarrhoea and vomiting, arthralgia.
- Recent trauma.
- Previous medical history, e.g. hypertension, IHD, stroke, DM, connective tissue diseases, immunosuppression.
- Drug history, e.g. phenytoin, isoniazid, vincristine, metronidazole.
- Social history, e.g. smoker (cord infarct), vegan (vitamin B₁₂ deficiency), travel history (infectious, e.g. TB, parasitic), sexual history (e.g. HIV).

Examination

- *What is the pattern of weakness?* Some common patterns, together with associated features, are illustrated under  Limb weakness: localizing the lesion, p. 358. This should help to localize the level of the lesion in the nervous system.
- *Is the weakness upper (UMN) or lower motor neuron (LMN)/combination?*
- *If UMN, is it pyramidal?* That is, extensor more than flexor weakness in the upper limbs, and flexor greater than extensor weakness in the lower limbs.
- *Is there fatiguable weakness with repetitive effort?* As in myasthenia.
- *Are there any involuntary movements?* Tremor [e.g. multiple sclerosis (MS)], myoclonic jerks, or fits (e.g. venous sinus thrombosis) may be noted.
- *What is the gait like?* This is important to test, if at all possible. It may demonstrate, for example, a hemiplegic gait, ataxia (cerebellar or sensory), a waddling (myopathic) gait, steppage (LMN) gait, or festinating movements of the parkinsonian patient.
- *Is there any sensory loss? Where? Is there a 'sensory level'?* Sensory changes are often the most difficult to elicit. Do not forget to test all modalities or to test the back of the legs up to the anal sphincter.
- *What modalities of sensation are lost?* Dorsal column loss produces a 'discriminatory' loss with impaired two-point discrimination, joint position and vibration loss, and sensory ataxia. Spinothalamic loss usually produces a lack of awareness of pain and temperature.

The history and examination should help to localize the lesion and, together with the patient's age, give an indication of the likely pathological process involved.⁴

Investigations

The initial investigation of choice depends upon the likely diagnosis. Investigations to consider are given in Box 6.2.

Diagnoses not to miss

- Spinal cord compression (➡ Spinal cord compression: assessment, p. 448).
- GBS (➡ Guillain–Barré syndrome, pp. 452–3).
- Subdural haematoma (➡ Subdural haematoma, pp. 400–1).
- Stroke (➡ Stroke: overview, pp. 412–13).

Diagnoses to consider

- Demyelination (MS, neuromyelitis, post-infectious, etc.).
- Malignancy (malignant meningitis, intracranial mass).
- Syringomyelia.
- Motor neuron disease.
- Vitamin deficiency (subacute combined degeneration—vitamin B₁₂).
- Peripheral neuropathy (toxic, DM, autoimmune, amyloid, etc.).
- TB, syphilis.

Box 6.2 Investigations to consider

- Blood tests: FBC, U&Es, LFTs, ESR, CRP, CK, glucose, PSA, B₁₂/folate, protein strip, syphilis serology, HIV, antiganglioside antibodies.
- CT scan.
- MRI brain ± spine.
- CSF analysis: protein, cells, microscopy, culture, sensitivity, glucose, oligoclonal bands.
- Visual-evoked potentials.
- Nerve conduction studies (NCS) and electromyography (EMG).
- Edrophonium test or ICE test.
- Muscle/nerve biopsy.

Practice points

A patient who can cycle easily, but only walk yards, usually has lumbar stenosis or parkinsonism.

References

4. Adapted from Lindsay KW, Bone I, Fuller G (2010). General approach to history and examination: In: Lindsay KW, Bone I, Callender R. *Neurology and Neurosurgery Illustrated*, 5th edn, pp. 1–2. Churchill Livingstone, London.

Limb weakness: localizing the lesion

For patterns of limb weakness, see Table 6.1.

Table 6.1 Patterns of limb weakness

Monoplegia	Lesion site	Other features
Arm ± face 	Contralateral cortex (e.g. stroke, tumour, or inflammation)	● Visual field defect ● Dysphasia (dominant hemisphere lesion) ● Cortical sensory loss (JPS and 2-point discrimination)
Leg only 	Contralateral cortex (e.g. anterior cerebral artery territory)	● With ipsilateral sensory deficit
	Ipsilateral spinal lesion (e.g. inflammation, injury, or tumour)	● Contralateral pain and temperature loss ● JPS lost on same side
Hemiplegia	Lesion site	Other features
Face + arm + leg 	Contralateral hemisphere (e.g. stroke, tumour, or inflammation)	● UMN CN VII involvement ● Impaired consciousness ● Visual field defect ● Dysphasia (if dominant hemisphere lesion)
	Contralateral internal capsule	● UMN CN VII involvement ● Alert ● No dysphasia (even with a dominant hemisphere lesion)
	Contralateral midbrain lesion (e.g. stroke, inflammation, tumour)	● Contralateral CN III palsy ● Impaired upgaze
Arm (± face) or leg alone 	Contralateral cortex	● CN VII unaffected ● Visual field defect ● Dysphasia (if dominant hemisphere lesion) ● Cortical sensory loss (↓ JPS and 2-point discrimination)
	Contralateral medullary	● Ipsilateral pain and temperature loss ● Contralateral Horner's syndrome ● Contralateral palatal and tongue weakness
	Ipsilateral spinal lesion	● Pain and temperature loss in contralateral leg ● Ipsilateral loss of JPS ● Ipsilateral Horner's
Arm, leg, and opposite face 	Contralateral pons	● LMN face involvement on opposite side to weak limbs ● Conjugate gaze deviation towards weak side

Table 6.1 (Contd.)

Hemiplegia	Lesion site	Other features
Arm and opposite leg 	Medullary lesion	● Palatal and tongue weakness on side of arm weakness
Paraplegia	Lesion site	Other features
	Midline cortical lesion	● Cortical sensory loss (JPS and 2-point discrimination) ● 'Frontal' incontinence ● Normal pain and temperature
	Thoracic spine	● 'Sensory level' ● Acute urinary retention or hesitancy of micturition
Tetraplegia	Lesion site	Other features
Face and all four limbs involved 	Pontine lesion	● 'Locked-in' syndrome: only vertical eye movements possible
Face spared 	Cervical spine lesion	● No CN lesion ● High lesions (C1–3) require ventilation ● Lesions at C4 have intact diaphragmatic breathing
	Medullary lesion	● No palatal or tongue movement or speech, but intact facial movements
Combined UMN and LMN signs		
		● LMN signs point to level of lesion ● Two lesions (e.g. cervical and lumbar spondylosis) may produce mixed signs in limbs
LMN limb weakness (unilateral or bilateral)		
		● Nerve root distribution? ● Plexopathy (suggested by involvement of contiguous nerve roots on one side)? ● Peripheral nerve distribution (mono- versus polyneuropathy) ● Presence of reflexes and normal sensation suggests myopathy (cf. neuropathy) ● Fatiguability suggests neuromuscular junction disease

CN, cranial nerve; JPS, joint position sense; LMN, lower motor neuron; UMN, upper motor neuron.

Acute dizziness: assessment

History

Determine whether:

- *There is true vertigo*, i.e. a sensation that either the patient or their environment is rotating. Distinguish this from 'light-headedness' more likely related to pre-syncope.
- *Symptoms started acutely* are progressively worsening or are transient (see 'vertebrobasilar TIAs' under ⚡ Transient ischaemic attacks, pp. 430–1). Vestibular neuritis typically begins over a period of a few hours, peaks in the first day, and then improves within days. Infarction causes a vestibular syndrome that typically has an abrupt onset. TIAs often last for <30min. Abrupt onset of vertigo for seconds after a change in head position is characteristic of benign paroxysmal positional vertigo.⁵
- *Symptoms worse with certain postures*: vertigo is worse with certain head positions in benign positional vertigo and some cases of central nystagmus (see Box 6.3). Postural hypotension is frequently caused by drugs and can be caused by acute blood loss; uncommonly, it is due to autonomic failure.
- *There is associated tinnitus* (as in Ménière's disease).
- *Hearing loss* is present in Ménière's disease, cerebellopontine angle lesions, e.g. acoustic neuroma (Vth, VIth, and VIIIth nerves + ataxia).
- *Ear discharge* may occur with middle ear disease.
- *Associated focal neurological symptoms*, e.g. unilateral weakness, clumsiness, paraesthesiae, or numbness.
- *Headache*: sudden onset in intracerebral haemorrhage; progressive with features of ↑ ICP in mass lesions (e.g. acoustic neuroma). History of migraine (suggesting migrainous vertigo).
- *Any recent head injury?*
- *Systemic symptoms*, e.g. weakness and lethargy in anaemia.
- *Previous medical/psychiatric history*, e.g. hypertension, IHD, DM, risk factors for stroke or TIAs (⚡ Transient ischaemic attacks, pp. 430–1), episodes of neurological disturbance, panic attacks, and anxiety.
- *Drug history* is pertinent to both true vertigo (e.g. phenytoin, gentamicin, furosemide) and dizziness (e.g. antihypertensives, antidepressants, drugs for Parkinson's disease, hypoglycaemics).

Examination

- *Ear*: is there a discharge? Is the tympanic membrane normal?
- *Neurological examination*: should discover whether there are any focal signs due to brainstem or cerebellar disease (⚡ Examination of brainstem function 1, pp. 460–1). Non-contiguous brainstem pathology may be due to patchy demyelination. Do not forget to assess the *corneal reflex*, the absence of which is one of the earliest signs of an ipsilateral acoustic neuroma. Observe the *gait*, if possible; it may be ataxic. Examine *extraocular eye movements*. Is there intranuclear ophthalmoplegia (vascular/demyelinating brainstem disease)? Examine carefully for *nystagmus* (see Box 6.3). *Hallpike manoeuvre* involves

positioning the patient's head over one side of the bed and watching for nystagmus. *Benign positional vertigo*: nystagmus develops after a brief delay, but it fatigues and, with repetition, adapts. *Central nystagmus*: no initial delay, fatiguability, or adaptation. *Head impulse test* involves the examiner holding the patient's head while the patient fixates on the examiner's nose; rapid, small left and right rotations of the head should not displace the patient's gaze from the examiner's nose; if it does, with a corrective 'catch-up' saccade, peripheral vestibular disturbance is likely on the side towards which the head was turned. *Fundoscopy* may reveal papilloedema (suggestive of an intracranial SOL) or optic atrophy (which occurs with previous demyelination in MS).

- *General examination*: measure BP lying and then after 3 and 5 min of standing (including pulse). Postural hypotension is a common cause of dizziness.

Box 6.3 Classification of nystagmus

- *Vestibular nystagmus* is due to dysfunction of the labyrinth or vestibular nerve. The slow phase is towards the lesion; the quick phase is away from the lesion. There may be rotatory nystagmus.
- *Central nystagmus* is due to brainstem dysfunction (vestibular nuclei or their connections); there may be no vertigo associated with this form of nystagmus. The nystagmus may be horizontal, vertical, or rotatory; sometimes it is present in one eye only. The quick phase is determined by the direction of the gaze: it is multi-directional.
- *Positional nystagmus* may occur in benign positional vertigo, but with repeated testing, it adapts. It may also occur with posterior fossa lesions, e.g. cerebellar lesions (the quick phase tends to be towards the lesion), in which there is no adaptation.

References

5. Hotson JR, Baloh RW. Acute vestibular syndrome. *N Engl J Med*. 1998;339:680–5.

Acute dizziness: management

Investigations

These depend upon the likely diagnosis.

- Cerebellopontine angle lesions, such as acoustic neuroma, may be imaged by *CT with contrast*, but in general, posterior fossa and brainstem disease is better appraised by *MRI scanning*.
- *Pure tone audiometry* is a sensitive way of detecting sensorineural loss.
- Measure *blood sugar* and *FBC*, if indicated.

For management, see Tables 6.2 and 6.3.

Table 6.2 Approach to true vertigo

Type of vertigo	Management
<i>Acute vestibular neuritis</i>	Bed rest, then vestibular rehabilitation Consider cyclizine or prochlorperazine (avoid prolonged use)
<i>Benign positional vertigo</i>	Avoid precipitating position Epley or Sermont manoeuvre
<i>Ménière’s disease</i> (sensorineural deafness and tinnitus)	Bed rest Consider cyclizine or prochlorperazine Pure tone audiometry ENT referral
<i>Middle ear disease</i>	ENT referral
<i>Brainstem/cerebellar disease</i> (stroke, see 🔄 Stroke: overview, pp. 412–13; demyelination; vertebrobasilar insufficiency; migraine; vasculitis)	Consider CT/MRI
<i>Cerebellopontine angle lesions</i> (e.g. acoustic neuroma)	Pure tone audiometry MRI scan of internal auditory meati

Table 6.3 Dizziness but no true vertigo

Type of dizziness	Management
<i>Hypotension</i>	Postural, cardiac, volume loss, or autonomic failure
<i>Anaemia</i>	FBC, blood film, other investigations as necessary
<i>Hypoglycaemia</i>	Diabetic on hypoglycaemics or insulin, insulinoma
<i>Hyperventilation</i>	Attempt to reproduce symptoms; explain
<i>Carotid sinus hypersensitivity</i>	See ➡ Sinus bradycardia or junctional rhythm, p. 88

Acute loss of vision

History

Determine whether:

- Visual loss is or was monocular or binocular, complete or incomplete, e.g. hemianopia, central or peripheral loss, haziness or complete obscuration of vision.
- Loss of acuity occurred instantly ('like a curtain'), as in amaurosis fugax.
- Period for which it lasted.
- There were any other associated visual symptoms, e.g. scintillations ('flashing lights and shapes') occur in migraine.
- The eye is painful and red.
- Headache or facial pain: unilateral or bilateral; migrainous features.
- Associated focal neurological symptoms, e.g. unilateral weakness, clumsiness, paraesthesiae, or numbness.
- Any recent trauma?
- Systemic symptoms, e.g. malaise, aches, and pains.
- Previous medical history, e.g. hypertension, IHD, DM, other risk factors for stroke or TIAs (➡ Transient ischaemic attacks, pp. 430–1), migraine, connective tissue diseases.

Examination

- *External appearance of the eye:* is it red (➡ Painful red eye: assessment, pp. 368–9)? Is there corneal clouding?
- *Visual acuity:* should be measured for each eye with a Snellen chart. Near vision should be tested (with newsprint, if necessary). If none of these are possible, the patient's acuity for counting the number of fingers or perceiving hand movement or light should be noted. Correct with glasses/contact lenses or pinhole. Ideally, colour vision should also be examined with Ishihara plates.
- *Plot the visual fields:* often careful bedside examination is sufficient; perimetry available in ophthalmological departments is more sensitive and should be done to document the defect and recovery. Loss of vision may be incomplete.
- *Is there an afferent pupillary defect?* (Swinging torch test.)
- *Fundoscopy:* may reveal a retinal embolus, changes of central/branch retinal artery occlusion, swollen or pale optic nerve head, papilloedema, or hypertensive changes.
- *Is the temporal artery tender?* It need not be in temporal arteritis.
- *Complete neurological examination:* is necessary to discover if there are any other associated signs (e.g. spasticity in MS).
- *Listen for carotid bruits:* although they may not be present in patients with symptomatic carotid stenosis.
- *Assess heart rhythm (including ECG) and cardiovascular system:* for a possible cardiogenic source of embolus.
- *Measure BP* lying and then after 3 and 5 min of standing (including pulse) *and blood sugar:* hypotension in the presence of arteriosclerosis can lead to occipital lobe ischaemia. Hypertension and DM are risk factors for TIAs.

Investigations

See ➡ Stroke: other investigations, p. 418.

NB An *ESR* and *CRP* should be performed in any patient aged >50 years who presents with monocular blindness and unilateral headache. It is rarely normal in temporal arteritis. If the ESR is elevated and the presentation is compatible with temporal arteritis, high-dose corticosteroid therapy should be considered (initially 60mg/day PO) because the other eye is also at risk of anterior ischaemic optic neuropathy.

Approach to acute/subacute visual loss

Monocular transient loss without prominent unilateral headache

- Amaurosis fugax (🔄 Transient ischaemic attacks, pp. 430–1): in the elderly, this may be due to embolism. In some younger patients, it is probably due to vasospasm (a diagnosis of exclusion).
- Hyperviscosity syndrome (e.g. polycythaemia, myeloma, sickle-cell anaemia), hypercoagulable state, vasculitis: blood film, protein electrophoresis, autoimmune screen, other haematological investigations as required (🔄 Hyperviscosity syndrome, p. 654).
- Postural hypotension (may exacerbate vertebrobasilar ischaemia): stop any exacerbating drugs. Exclude autonomic neuropathy.

Monocular transient loss with prominent headache

- Migraine (usually there are symptoms such as nausea, sensory sensitivity, movement aggravation of headache, and positive visual phenomena, e.g. scintillations): observe, give analgesics/ergot derivative. Arrange neurological consultation.
- Giant cell arteritis [temporal artery tenderness, non-pulsatile, jaw claudication, fever, symptoms of polymyalgia rheumatica (PMR), raised ESR]. Start steroids and refer for urgent biopsy.

Monocular sustained loss with red eye

- Acute glaucoma (dilated pupil and corneal clouding): urgent ophthalmology referral.
- Acute uveitis (inflammation of the iris and ciliary body, with small pupil), keratitis (corneal inflammation), endophthalmitis (involvement of the vitreous, uvea, and retina, with cellular debris/pus in the anterior chamber), or ocular trauma: urgent ophthalmic referral.

Monocular sustained loss without red eye

Central scotoma with relative afferent pupillary defect

- Optic neuritis (orbital pain exacerbated by eye movement, reduced acuity and colour vision, inflamed disc unless retro-orbital) : the most common cause is demyelination, but consider the possibility of mass lesions compressing the optic nerve (consider evoked potentials, axial MRI orbit). Anterior ischaemic optic neuropathy (acutely inflamed optic disc) due to presumed atherosclerosis of posterior ciliary arteries or to temporal arteritis (temporal artery tenderness, non-pulsatile, jaw claudication, fever, symptoms of PMR, raised ESR): start steroids and refer for urgent biopsy.

Central scotoma without relative afferent pupillary defect

- Vitreous haemorrhage.
- Macular disorder: macular degeneration, haemorrhage, or exudate.
- Branch or central retinal vein/artery occlusion (see Fig. 6.1).

Peripheral visual field loss

- Retinal detachment.
- Chorioretinitis.
- Intraocular tumour.
- Retinal vascular occlusion.

Binocular sustained loss

- Field loss, e.g. quadrantanopia (stroke, tumour, inflammation), hemianopia, bitemporal (pituitary lesions): initially CT scan.
- Hypotension (e.g. cardiac failure).
- Basilar artery thrombosis : dysrhythmias or vertebrobasilar insufficiency may produce transient episodes of binocular visual loss. CT scan.
- Posterior reversible encephalopathy syndrome (PRES) with headaches, confusion, seizures, and visual loss: triggered by hypertension, renal failure, eclampsia, and immunosuppressants. Improves over days or weeks. MRI brain required.
- Toxic optic neuropathies (e.g. tobacco, alcohol, methanol).
- Genetic (e.g. Leber's hereditary optic neuropathy).

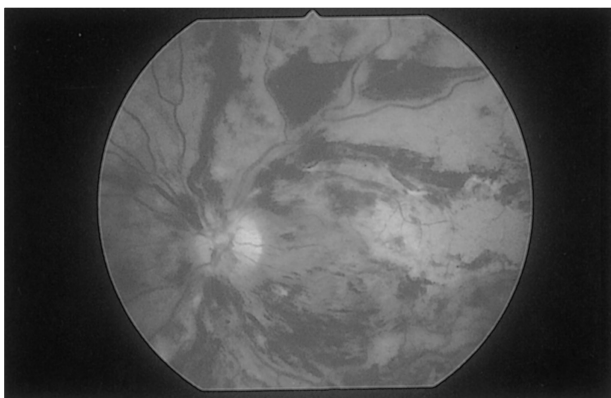


Fig. 6.1 Central retinal vein occlusion with assorted closure of the arterial circulation above the macula (➡ Approach to acute/subacute visual loss, pp. 366–7).

Reproduced from Easty D, et al. *Oxford Textbook of Ophthalmology*, 1999, with permission from Oxford University Press.

Painful red eye: assessment

For a differential diagnosis of the 'red eye', see Table 6.4.

History

This should establish if there has been:

- *Ocular trauma or foreign body (including contact lens) in the eye.*
- *Sudden or gradual onset of symptoms, and nature and location of pain:* irritation, soreness, or gritty sensations may occur with conjunctivitis, but the pain is severe in acute glaucoma.
- *Diminution of visual acuity:* occurs with conditions affecting the cornea (variable reduction), iris (mild reduction), and glaucoma (severe reduction of acuity).
- *Discharge (not simply lacrimation) from eyes:* may be mucopurulent with bacterial or chlamydial conjunctivitis. It may be mucid and stringy with allergic conditions or dry eyes.
- *Headache or facial pain:* is common with orbital cellulitis. It may precede cavernous sinus thrombosis (IIIrd, IVth, V₁, V₂, VIth nerves) or herpes zoster ophthalmicus.
- *Photophobia:* suggests corneal involvement or iritis.
- *Systemic symptoms, e.g. malaise/fever:* occurs with orbital cellulitis and cavernous sinus thrombosis; vomiting is a feature of acute glaucoma, arthralgias + urethral discharge suggests Reiter's or chlamydial infection.
- *Previous history:* recurrent red eyes may occur with episcleritis, iritis, and herpes simplex corneal ulcer. Ask specifically about BP, heart disease, DM, connective tissue diseases, and atopy.

Examination

- *What is red?* The conjunctiva, iris, sclera or episclera (which lies just beneath the conjunctiva and next to the sclera), eyelid, skin around the orbit? Is there visible haemorrhage, either subconjunctival or in the anterior chamber (hyphaema)? In conjunctivitis, there is 'injection', or filling of existing light red vessels, with individual branches distinctly visible; the vessels can be moved with the conjunctiva over the sclera. Ciliary or circumcorneal injection refers to a blue-red discoloration, most conspicuous at the limbus (cornea-scleral border) and occurs in anterior uveitis or iritis and keratitis (corneal inflammation). Mixed injection (conjunctival + ciliary) also occurs in uveitis.
- *Is there proptosis?* Suggests a retro-orbital/intraorbital mass or cavernous sinus thrombosis, in which it may become bilateral.
- *Is it pulsatile?* As in a carotid-cavernous fistula, with an audible bruit.
- *Is there ophthalmoplegia?* (Mass lesion or cavernous sinus thrombosis.)
- *Is visual acuity diminished?* A Snellen chart should be used and near vision tested (with newsprint, if necessary). In acute glaucoma, there is marked reduction in acuity; in acute iritis or keratitis, acuity is only modestly diminished; in conjunctivitis, it is normal. Orbital apex lesions (anterior to the cavernous sinus) may present similarly to cavernous sinus pathology, with additional acuity loss).
- *What is the size of the pupil?* Fixed and dilated in acute glaucoma; small with reduced reaction to light in iritis; normal in conjunctivitis.
- *Is the red reflex normal? If it is, does the cornea appear normal?* The red reflex may be impaired in keratitis, central corneal ulcer or oedema, anterior chamber hyphaema (blood in the anterior chamber after blunt trauma), anterior uveitis, glaucoma, or endophthalmitis (involvement of the vitreous,

uvea, and retina, with cellular debris/pus in the anterior chamber). *Fundoscopy* may not be possible as with the corneal clouding of acute glaucoma.

- *Are there any anterior chamber abnormalities?* In acute anterior uveitis, there are exudates in the anterior chamber.
- *Is there a rash or vesicles on the face, nose, or eyelid?* Herpes zoster can lead to conjunctivitis, iritis, corneal ulceration, and secondary glaucoma.

Table 6.4 Differential diagnosis of the 'red eye'^{*}

	Conjunctiva	Iris	Pupil	Cornea	Anterior chamber	Intraocular pressure	Appearance
Acute glaucoma	Both ciliary and conjunctival vessels injected. Entire eye is red	Injected	Dilated, fixed, oval	Steamy, hazy	Very slow	Very high	
Iritis	Redness most marked around cornea Colour does not blanch on pressure	Injected	Small, fixed	Normal	Turgid	Normal	
Conjunctivitis	Conjunctival vessels injected, greatest towards fornices Blanch on pressure Mobile over sclera	Normal	Normal	Normal	Normal	Normal	
Subconjunctival haemorrhage	Bright red sclera with white rim around limbus	Normal	Normal	Normal	Normal	Normal	

^{*} Reproduced with permission from Judge RD et al. (1989). *Clinical Diagnosis*, 5th edn.

Painful red eye: management

With a careful history and examination, the diagnosis may become clear. *Unless you are absolutely sure of the diagnosis, discuss the patient with an ophthalmologist.*

Diagnosis of painful red eye in non-traumatic cases

With prominent ocular discharge

- Viral/bacterial conjunctivitis (watery/mucopurulent discharge, normal red reflex, normal pupil).
- Bacterial/fungal keratitis (mucopurulent discharge, opaque cornea with impaired red reflex, normal or slightly reduced pupil).
- Keratoconjunctivitis sicca or atopic response (dry eye, mucoid strands).

Without prominent discharge and normal red reflex

Normal cornea

- Episcleritis, scleritis, or subconjunctival haemorrhage.
- Orbital cellulitis (skin around the orbit is erythematous and tender).
- Carotid–cavernous fistula (dilated conjunctival vessels, forehead veins, and choroidal vessels because of ‘arterialization’, reduced acuity because of optic nerve ischaemia, pulsatile proptosis, and bruit).
- Cavernous sinus thrombosis (fever, acute onset, painful ophthalmoplegia, conjunctival oedema and congestion, proptosis, oedema over mastoid (emissary vein), may progress to meningitis).

Abnormal cornea

Corneal abrasion or ulcer (NB herpes simplex and herpes zoster).

Without prominent discharge and impaired red reflex

- Acute glaucoma (severe pain, markedly reduced acuity, cloudy cornea, purple congestion at limbus, fixed dilated pupil, rock-hard globe).
- Acute anterior uveitis (malaise, clear cornea, blue–red congestion at limbus, anterior chamber exudate, iris muddy and injected, small pupil with reduced response to light).
- Endophthalmitis (reduced acuity, eyelid swelling, conjunctival injection, anterior chamber cellular debris, vitreous clouding, retinal haemorrhages).
- Keratitis (red congestion at limbus, pupil normal or reduced in size, cornea opaque).
- Central corneal ulcer.

Acute bacterial meningitis: assessment

Presentation

- Headache, fever, neck stiffness (absent in some patients),⁶ photophobia (often over hours to days).
- Rash: meningococcal meningitis is most commonly associated with a macular rash progressing to petechiae or purpura (➡ Meningococcal infection: assessment, pp. 486–7), but other organisms may also cause a rash.
- Confusion, psychiatric disturbance (e.g. mania) or altered level of consciousness: in the elderly (especially those with DM or cardiopulmonary disease) and the immunocompromised or neutropenic, there may be little other than confusion.
- Focal neurological signs: complicate meningitis in at least 15% of cases. These can suggest cerebral damage (e.g. hemiparesis following venous infarction or arteritis) or indicate cranial nerve and brainstem involvement by basal exudation and inflammation (e.g. in *Listeria monocytogenes* meningitis). They can also indicate brain shift secondary to raised ICP (➡ Examination of brainstem function 3, pp. 464–5). Consider the possibility of brain abscess or encephalitis if focal signs or seizures are prominent. Papilloedema is uncommon (<1%) and should suggest an alternative diagnosis.
- Seizures: are the presenting feature in up to 30%.

Predisposing factors

Usually none, but acute otitis media, mastoiditis, pneumonia, head injury, sickle-cell disease, alcoholism, previous influenza infection, and immunocompromised states are all associated.

Causes in adults

Common

- *Neisseria meningitides*.
- *Streptococcus pneumoniae*.

Rarer

- Gram-negative bacilli (in elderly).
- *Listeria* (in elderly).

Assessment of severity

Mortality ↑ as consciousness ↓ (~55% for adults in coma). However, meningitis can proceed with alarming rapidity, even in the most alert patients.

Management

- 1 Stabilize the patient (Airway, Breathing, Circulation); give O₂.
- 2 Commence antibiotics. It is *not* necessary to await CSF analysis.
- 3 CT scan prior to LP (this is the safest option).
- 4 Make a definitive diagnosis with LP.
- 5 Reconsider antibiotic regimen after CSF analysis. Consider adjunctive corticosteroid therapy.
- 6 Arrange for contacts (including medical/nursing staff) to have prophylaxis. Notify the public health service.
- 7 Observe for and, if necessary, treat complications.

References

6. Brouwer MC, Thwaites GE, Tunkel AR, van de Beek D. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. *Lancet* 2012;**380**:1684–92.

Acute bacterial meningitis: immediate management

For management of bacterial meningitis, see Box 6.4.

Antibiotic therapy: follow your hospital guidelines if available

- Adults aged between 18 and 50 should receive *cefotaxime* 2g qds or *ceftriaxone* 2g every 12h. For adults aged over 55 without a rash, consider the addition of 2g ampicillin every 6h to cefotaxime or ceftriaxone as above (to cover *Listeria*). If the patient comes from an area of the world where penicillin and cephalosporin-resistant pneumococci are common (e.g. Mediterranean countries), then add IV *vancomycin* 500mg every 6h ($\pm$ *rifampicin*). If the individual is allergic to penicillin, consider IV *chloramphenicol* 25mg/kg every 6h with *vancomycin* 500mg every 6h. Additional co-trimoxazole should be given in those over 50. Discuss the case with your microbiologist.
- *Blood cultures* should be taken, but it is dangerous to withhold IV antibiotics until these are taken or an LP is performed. Most organisms will be diagnosed from blood cultures.
- Meningococcal infections are discussed under ➡ Meningococcal infection: assessment, pp. 486–7.

CT scan

Our policy is that all patients should have a CT scan prior to LP. Others suggest this needs be performed only if there is ↓ level of consciousness, focal signs, papilloedema, or signs suggesting impending cerebral herniation (➡ Examination of brainstem function 3, pp. 464–5). You should discuss the patient with a senior member of your team.

Lumbar puncture

- *Measure opening pressure*: CSF pressure is often raised (>20 cm CSF) in meningitis, and there are only a few reports of cerebral herniation (coning) following the procedure. If the pressure is raised, the patient must be observed closely at no less than 15-min intervals. A CT scan is required to exclude a complication of meningitis or an SOL, e.g. cerebral abscess.
- *Analysis of CSF* (see Table 6.5):
 - *CSF WCC*: bacterial meningitis characteristically demonstrates a high (usually $>1000/\text{mm}^3$) WCC with predominance of neutrophils. A low CSF WCC ($0\text{--}20/\text{mm}^3$) with a high bacterial count on Gram stain is associated with a poor prognosis.
 - *CSF glucose*: usually reduced (CSF:blood glucose ratio <0.3 in 70%) but may be normal.
 - *CSF protein*: usually elevated ($>1.0\text{g/L}$).
 - *Gram stain*: is positive in 60–90% but may not be if there has been a delay between starting antibiotics and LP. Also the yield of CSF culture falls to $<50\%$ from 70–85%.

This CSF profile may also occur with viral and TB meningitis in the early phase, but repeat CSF analysis shows transformation to a lymphocytic

predominance. Patients with a CSF profile characteristic of bacterial meningitis should be treated as if they have this condition until proven otherwise.

Table 6.5 CSF composition in meningitis

	Bacterial	Viral	TB meningitis
Appearance	Turbid	Clear	Clear
Cells (per mm ³)	5–2000	5–500	5–1000
Main cell type	Neutrophil	Lymphocyte	Lymphocyte
Glucose (mmol/L)	Very low	Normal	Low
Protein (g/L)	Often >1.0	0.5–0.9	Often >1.0
Other tests	Gram stain Bacterial antigen	PCR	ZN Fluorescence test PCR

See  Lumbar puncture 2, p. 858 for reference intervals for CSF analysis.

Box 6.4 Management key points: bacterial meningitis

- GPs should give benzylpenicillin or a third-generation cephalosporin (cefotaxime or ceftriaxone) before urgent transfer to hospital. Give chloramphenicol if there is a history of anaphylaxis to penicillin or cephalosporins.
- Initial blind therapy: third-generation cephalosporin (cefotaxime 2g qds or ceftriaxone 2g bd).
- Meningococci: benzylpenicillin or third-generation cephalosporin for at least 5 days (chloramphenicol if there is history of anaphylaxis to these). Give rifampicin for 2 days to patients treated with benzylpenicillin or chloramphenicol (to eliminate nasopharyngeal carriage).
- Pneumococci: third-generation cephalosporin or benzylpenicillin (if penicillin-sensitive) for 10–14 days. If penicillin- and cephalosporin-resistant pneumococci: add vancomycin (+ if necessary rifampicin).
- *Haemophilus influenzae*: third-generation cephalosporin for at least 10 days (chloramphenicol if there is a history of anaphylaxis to penicillin or cephalosporins or if the organism is resistant to these).
- *Listeria*: amoxicillin ± gentamicin.
- Adjunctive dexamethasone in suspected pneumococcal or *H. influenzae* meningitis. Avoid in septic shock, meningococcal disease, immunocompromised patients, or meningitis following surgery.
- Notify public health services, and consult a consultant in communicable disease control for advice regarding chemoprophylaxis and vaccination for close contacts:
 - *Neisseria meningitidis* (to eradicate pharyngeal carriage) in adults: rifampicin (600 mg PO, every 12h, total of four doses) or ciprofloxacin (500 mg PO once) or ceftriaxone (250 mg IM once)
 - *H. influenzae*: rifampicin (600mg od for 4 days in adults).

Acute bacterial meningitis: continuing therapy

Reconsider antibiotics? Adjunctive steroids?

- *CSF lymphocytosis*: if the CSF pleocytosis is predominantly lymphocytic, the diagnosis is unlikely to be bacterial meningitis. This is discussed further under ➡ Meningitis with lymphocytic CSF, pp. 376–7.
- *CSF polymorphs* $>50\,000/\text{mm}^3$: suggests possibility of cerebral abscess. A CT brain scan should be performed.
- *CSF Gram stain*: if Gram –ve diplococci are visible, continue with 2.4g *benzylpenicillin* IV every 4h or 2g *ampicillin* IV 4-hourly. Discuss the case with your microbiologist. If Gram +ve diplococci are visible, give 2g *cefotaxime* IV 6-hourly and consider adding *vancomycin* 500mg IV 6-hourly. If Gram +ve cocco-bacilli suggestive of *L. monocytogenes* are visible, give *ampicillin* 2g 4-hourly IV and *gentamicin* 5mg/kg/24h IV as a single daily dose or divided into 8-hourly doses.
- *Adjunctive corticosteroid therapy*: has been shown to reduce the incidence of neurological sequelae in adults and children, especially in pneumococcal meningitis,⁸ and many neurologists now favour its use to reduce inflammation. In patients with raised ICP, stupor, or impaired mental status, give 10mg dexamethasone IV loading dose, followed by 4–6mg PO qds.

Prophylaxis for contacts should be given immediately

- *Public health services* should be notified of any case of bacterial meningitis. They will be able to give advice on current prophylactic treatment and vaccination (possible with some strains of meningococcus); they will also assist in contact tracing. Patients with meningococcus are infectious and can spread organisms to others. Liaise with your local microbiologists.
- *Prophylaxis* should be given as soon as the diagnosis of bacterial meningitis is suspected. In the UK, for adult contacts, rifampicin 600mg bd for 2 days is recommended. An alternative for adults is ciprofloxacin 750mg as a single dose (for children older than 1 year: 10mg/kg bd for 2 days; for children 3 months–1 year: 5mg/kg bd for 2 days).

References

8. Brouwer MC, Thwaites GE, Tunkel AR, van de Beek D. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. *Lancet* 2012;**380**:1684–92.

Acute bacterial meningitis: complications and their treatment

- *Raised ICP* may respond to steroids and, as discussed earlier, some neurologists give this routinely to reduce inflammatory reaction. In the acute situation, if there is clinical evidence of brain shift or impending transtentorial herniation (➡ Examination of brainstem function 3, pp. 464–5), mannitol should be given 1g/kg over 10–15min (~250mL of 20% solution for an average adult) and the head of the bed elevated to 30° (➡ Measures to reduce ICP, p. 390). A preference of hypertonic 3% normal saline may be used to maintain $\text{Na}^+ > 145$ or serum Osm > 290 .
- *Hydrocephalus* (diagnosed by CT) may require an intraventricular shunt and should be discussed urgently with neurosurgeons. It can occur because of thickened meninges obstructing CSF flow or because of adherence of the inflamed lining of the aqueduct of Sylvius or fourth ventricular outflow. Papilloedema may not be present.
- *Seizures* should be treated as for seizures of any other aetiology (➡ Status epilepticus (tonic–clonic) 1, pp. 408–9).
- *Persistent pyrexia* suggests that there may be an occult source of infection. The patient should be carefully re-examined (including oral cavity and ears).
- *Focal neurological deficit* may occur because of arteritis or venous infarction or an SOL, e.g. subdural empyema. Basal meningitis may lead to cranial nerve palsies. A CT scan should be requested if it has not already been performed.
- *Subdural empyema* is a rare complication. Focal signs, seizures, and papilloedema suggest the diagnosis. It requires urgent surgical drainage.
- *DIC* is an ominous sign. Platelet and FFP may be required. The use of heparin should be discussed with a haematologist and neurologist.
- *Syndrome of inappropriate antidiuretic hormone secretion (SIADH)* may occur. Fluid balance and electrolytes need to be checked regularly.

Meningitis with lymphocytic CSF

Presentation

- Viral meningitis may be indistinguishable on clinical grounds from acute early bacterial meningitis, but it is usually self-limiting.
- TB meningitis is usually preceded by a history of malaise and systemic illness for days to weeks before meningeal features develop. However, it may present very acutely. TB meningitis may be associated with basal arachnoiditis, vasculitis, and infarction, leading to focal neurological signs, e.g. cranial nerve palsies, obstructive hydrocephalus with papilloedema.
- Cryptococcal or syphilitic meningitis in the immunocompromised present with features indistinguishable from TB meningitis.
- Malignant meningitis (including metastases and lymphoma) may present with constitutional features. CSF cytology in large volumes and often repeated samples are needed for diagnosis.

Causes

Viral

- Coxsackie.
- Echo.
- Mumps.
- Herpes simplex type 1.
- Varicella-zoster.
- HIV.
- Lymphocytic choriomeningitis virus.

Non-viral

- TB.
- *Cryptococcus*.
- Leptospirosis.
- Lyme disease.
- Syphilis.
- Brucellosis.
- Parameningeal infection with a CSF reaction.

CSF findings

The CSF usually demonstrates lymphocytosis. but the CSF in viral meningitis may initially demonstrate predominantly neutrophils. It is important not to dismiss the possibility of TB meningitis if CSF glucose is normal; the tuberculin test may also be negative initially. *Mycobacterium tuberculosis* is seen in the initial CSF of ~40% of patients with TB meningitis. Send CSF for viral and TB PCR (the latter is specific, but not sensitive enough to rule out if not present when clinically likely).

Treatment regimens

- *Viral meningitis*: usually supportive treatment only. Treat with aciclovir only if encephalitic features (e.g. confusion, seizures).
- *TB meningitis*: for 2 months—rifampicin (450mg/day if weight <50kg or 600mg/day if weight >50kg; many clinicians give up to 2–3 times the dose), ethambutol (15mg/kg/day), pyrazinamide (1.5g/day if weight <50kg; 2g/day if weight >50kg), and isoniazid 300mg/day (double if severely unwell). Then continue rifampicin and isoniazid alone for further 7–10 months. Give treatment IV if any concern about absorption PO/NG. Give pyridoxine 10mg daily as prophylaxis against isoniazid neuropathy. Adjunctive prednisolone from start (2.5mg/kg/day IV, then PO) for 4 weeks (then 4-week taper), regardless of severity. Consult your local respiratory/ID specialists for advice. Test HIV status.

- *Cryptococcal meningitis*: several regimens are used. Amphotericin 0.7–1.0mg/kg/day alone (divided into four daily doses). Ensure good hydration and monitor renal function. Fluconazole (1200mg/day initially) is an alternative if amphotericin is not available.

Further reading

Thwaites GE, van Toorn R, Schoeman J. Tuberculous meningitis: more questions, still too few answers. *Lancet Neurol* 2013;**12**:999–1010.

Acute viral encephalitis

Presentation

- *Change in personality.*
- *Confusion, psychiatric disturbance, or altered level of consciousness.*
- *Headache, fever, and some neck stiffness:* meningism is usually not prominent—some individuals have meningoencephalitis.
- *Focal neurological signs:* hemiparesis or memory loss (usually indicative of temporal lobe involvement) is not uncommon.
- *Seizures:* are common; some are complex partial in nature.
- *Raised ICP and signs of brain shift* (➡ Examination of brainstem function 3, pp. 464–5).
- *Predisposing factors:* immunocompromised patient.

For autoimmune and paraneoplastic encephalitis, see Box 6.5.

Management

(See Box 6.6.)

1. Antibiotic therapy

If there is any suspicion that the illness is meningitis, start antibiotics (➡ Acute bacterial meningitis: immediate management, pp. 372–3). It is not necessary to await CSF analysis.

2. Specific antiviral therapies

Aciclovir has dramatically reduced mortality and morbidity in HSV encephalitis. Most clinicians therefore give it in suspected encephalitis, without waiting for confirmation that the pathogen is herpes simplex.

- *Aciclovir* 10mg/kg IV (infused over 60min) every 8h (reduced dose in renal insufficiency) is given for 10–14 days.
- *Ganciclovir* 2.5–5.0mg/kg IV (infused over 60min) every 8h should be given if CMV is a possible pathogen (more likely in renal transplant patients or those with AIDS). Treatment is usually for 14–28 days, depending upon the response.

3. CT scan: scan all patients prior to LP

In a patient with focal neurological signs, focal seizures, or signs of brain shift, a CT scan must be arranged urgently. CT may not demonstrate any abnormalities. In herpes simplex encephalitis, there may be low-attenuation areas, particularly in the temporal lobes, with surrounding oedema. MRI is more sensitive to these changes.

4. Lumbar puncture

- *Measure opening pressure.* CSF pressure may be raised (>20cm CSF), in which case the patient must be observed closely at 15-min intervals.
- *Analysis of CSF* usually reveals lymphocytic leucocytosis (usually 5–500/mm³) in viral encephalitis, but it may be entirely normal. The red cell count is usually elevated. PCR on CSF is sensitive and specific. CSF protein is only mildly elevated, and glucose is normal.

5. Further investigations

- **Serology:** save serum for viral titres (IgM and IgG). If infectious mononucleosis is suspected (see Fig. 6.2), a monospot test should be performed.
- **EEG:** should be arranged, even in those without seizures. There may be generalized slowing, and in herpes simplex encephalitis, there may be bursts of periodic high-voltage slow-wave complexes over the temporal cortex.

Complications

Neurological observations should be made regularly. Two complications may require urgent treatment.

- **Raised ICP** due to cerebral oedema may require treatment with dexamethasone (➡ Intracranial space-occupying lesion, pp. 394–5). In the acute situation, if there is evidence of brain shift, mannitol may be used (➡ Measures to reduce ICP, p. 390). Another cause of raised ICP is haemorrhage within necrotic tissue. Perform a CT scan if there is any deterioration in the patient, and discuss with neurosurgeons.
- **Seizures** may be difficult to control but are treated as seizures of any other aetiology.

Causes in the UK

- Herpes simplex.
- Varicella-zoster.
- Coxsackie.
- CMV (in immunocompromised).
- Mumps.
- EBV.
- Echovirus.

Box 6.5 Autoimmune and paraneoplastic encephalitis

- A group of conditions due to antibodies against cell surface markers or immune responses against intracellular targets that tend to be subacute (over weeks) and can mimic infectious encephalitis.
- Symptoms are broad and include psychiatric manifestations (psychosis, catatonia), seizures, amnesia, altered consciousness, dysautonomia, and movement disorders.
- MRI brain, CSF (possible mild lymphocyte and protein rise). Antibodies (e.g. VGKC associated antibodies, NMDA) in serum or CSF.
- Treat with IV immunoglobulin or steroids. May be paraneoplastic, so search for cancer and treat appropriately.

Box 6.6 Management key points: viral encephalitis

- **Antiviral therapy:** aciclovir without waiting for confirmation of HSV—10mg/kg IV infused over 60min tds (reduced dose in renal insufficiency) for 10–14 days. Ganciclovir if CMV is a possible pathogen (renal transplant patients or in AIDS).
- **Antibiotics:** if there is any suspicion of meningitis. Do not delay treatment because of investigations (i.e. CT and LP).

Head injury: presentation

For symptoms following a head injury, see Box 6.7.

- Varies from transient 'stunning' for a few seconds to coma.
- A fraction of patients who attend A&E need to be admitted for observation (indications for admission are given in Box 6.12).

In the alert patient, determine the following.

- *Circumstances surrounding injury.* Was it caused by endogenous factors, e.g. loss of consciousness while driving? Or exogenous factors, e.g. another driver? Was there extracranial trauma?
- *Period of loss of consciousness.* This relates to the severity of diffuse brain damage.
- *Period of post-traumatic amnesia.* The period of permanent memory loss after injury also reflects the degree of damage. (NB The period of retrograde amnesia or memory loss for events prior to injury does not correlate with the severity of brain damage.)
- *Headache/vomiting.* Common after a head injury, but if they persist, raised ICP should be considered (➡ Raised intracranial pressure, pp. 388–90).
- *GCS score.*
- *Skull fracture present?*
- *Neurological signs.* Are there any focal neurological signs?
- *Extracranial injury.* Is there evidence of occult blood loss?

The drowsy or unconscious patient needs the following:

- *Urgent assistance from senior A&E staff and anaesthetists.*
- *Protection of airway:* the patient who has deteriorating level of consciousness or is in coma should be intubated because hypocarbia and adequate oxygenation are effective means of reducing ICP rapidly. If the patient is neurologically stable and protecting their airway, intubation may not be necessary. Assume there is a cervical spine injury until an X-ray (of all seven cervical vertebrae) demonstrates otherwise.
- *Hyperventilation:* the pattern of breathing should be noted (➡ Examination of brainstem function 2, p. 462). Hyperventilation of intubated patients with the aim of lowering $P_a\text{CO}_2$ is controversial—consult an intensivist.
- *Support of circulation:* hypotension should be treated initially with colloid. If persistent or severe, exclude a cardiac cause (ECG) and occult haemorrhage (e.g. intra-abdominal).
- *Treatment of seizures:* diazepam 5–10mg IV/PR, which may be repeated to a maximum of 20mg. If seizures continue, consider IV phenytoin (➡ Status epilepticus (tonic-clonic) 1, pp. 408–9).
- *Rapid survey of the chest, abdomen, and limbs:* looking for a flail segment or haemo-/pneumothorax, possible intra-abdominal bleeding (if there are any doubts, peritoneal lavage may be required), limb lacerations, and long bone fractures.
- *Brief history:* should be obtained from the ambulance crew or relatives. The patient may have lost consciousness just before the injury, e.g. due to SAH, seizure, or hypoglycaemia. The tempo of neurological deterioration should be established.
- *Guidelines for performing skull X-rays and CT head scans:* see ➡ Head injury: assessment, p. 382.

Box 6.7 Symptoms following head injury*Symptoms associated with minor head injury*

Headache, dizziness, fatigue, reduced concentration, memory deficit, irritability, anxiety, insomnia, hyperacusis, photophobia, depression, and general slow information processing.

Symptoms associated with moderate to severe head injury

As for minor head injury, but also:

- *Behavioural problems*, including irritability, impulsivity, egocentricity, emotional lability, impaired judgement, impatience, anxiety, depression, hyper- or hyposexuality, dependency, euphoria, aggressiveness, apathy, childishness, and disinhibition.
- *Cognitive impairment*, including deficits of memory, difficulty in abstract thinking, general slow information processing, poor concentration, slow reaction time, impaired auditory comprehension, reduced verbal fluency, anomia, and difficulty planning or organizing.

Practice points

- Younger patients after head injury typically present with extradural haemorrhage, while subdural haemorrhage is more common in the elderly.

Head injury: assessment

Examination

Rapid neurological assessment should take only a few minutes

- The level of consciousness must be noted with the GCS score (➡ Glasgow Coma Scale (GCS), p. 458).
- Note the size, shape, and reactions of the pupils to bright light.
- Resting eye position and spontaneous eye movements should be observed. If the latter are not full and the patient is unresponsive, test oculoccephalic and/or oculovestibular responses (➡ Oculocephalic and oculovestibular responses, pp. 466–7).
- The doll's head manoeuvre should not be attempted if cervical spine injury has not been excluded.
- Test the corneal reflex [cranial nerves V (sensory) and VII (motor)].
- Motor function should be assessed (➡ Glasgow Coma Scale (GCS), p. 458); any asymmetry should be noted.
- Look for features suggesting brain shift and herniation (➡ Examination of brainstem function 3, pp. 464–5).

Head and spine assessment

- The skull should be examined for a fracture. Extensive periorbital haematomas, bruising behind the ear (Battle's sign), bleeding from the ear, and CSF rhinorrhoea/otorrhoea suggest a basal skull fracture. Look for facial (maxillary and mandibular) fractures.
- Only 1% of patients will have a skull fracture. This greatly increases the chances of an intracranial haematoma (from 1:1000 to 1:30 in alert patients; from 1:100 to 1:4 in confused/comatose patients). NB Potentially fatal injuries are not always associated with skull fracture.
- Consider the possibility of spinal cord trauma. 'Log-roll' the patient, and examine the back for tenderness over the spinous processes, paraspinal swelling, or a gap between the spinous processes. The limbs may have been found to be flaccid and unresponsive to pain during the neurological assessment. There may be painless retention of urine.

For indications for skull X-ray, see Box 6.8.

Do not use plain X-rays of the skull to diagnose significant brain injury without prior discussion with a neuroscience unit. However, they are useful as part of the skeletal survey in children presenting with suspected non-accidental injury.

For definite indications for CT scan, see Box 6.9.

For things to look for on C-spine films, see Box 6.10.

Box 6.8 Indications for skull X-ray

- Do not use plain X-rays of the skull to diagnose significant brain injury without prior discussion with a neuroscience unit. However, they are useful as part of the skeletal survey in children presenting with suspected non-accidental injury.

Box 6.9 Definite indications for CT scan

- Focal neurological deficit.
- Depressed level of consciousness and/or neurological dysfunction (including seizures), GCS score <13 on initial assessment in the emergency department, GCS score <15 at 2h after the injury on assessment in the emergency department.
- Any sign of basal skull fracture (haemotympanum, 'panda' eyes, CSF leakage from the nose or ear, Battle's sign).
- Suspected open or depressed skull fracture.
- Post-traumatic seizure.
- >1 episode of vomiting.

For further information, see NICE clinical guideline CG176, 2017 (<https://www.nice.org.uk/guidance/cg176>).¹¹

Box 6.10 Things to look for on C-spine films

- Check all seven C-spine vertebrae and C7–T1 junction are visible.
- Check alignment:
 - Anterior and posterior aspects of vertebral bodies.
 - Posterior margin of the spinal canal.
 - Spinous processes.
- A step of >25% of a vertebral body suggests facet joint dislocation.
- Check contours:
 - Outlines of vertebral bodies.
 - Outlines of spinous processes.
- Look for avulsion fractures, wedge fractures (>3mm height difference between the anterior and posterior body heights).
- Check the odontoid:
 - Open mouth and lateral views.
- The distance between the ant. arch C1 and odontoid should be <3mm disc space and odontoid:
 - Disc spaces.
 - Space between anterior C3 and back pharyngeal shadow >5mm suggests retropharyngeal mass (e.g. abscess or haematoma from fracture of C2).
- Check soft tissues.

References

11. National Institute for Health and Care Excellence (2014). *Head injury: assessment and early management*. Clinical guideline [CG176]. <https://www.nice.org.uk/guidance/cg176>

Head injury: immediate management

- After resuscitation, *take blood* for FBC, G&S, U&Es, ABGs, and, if the circumstances of injury are not clear or there is a suspicion of drug intoxication, *toxicology screen*.
- For indications for admission, see Box 6.11.
- *Subsequent management* depends upon the pace of events and the clinical situation; >40% of comatose patients with head injury have intracranial haematomas, and it is not possible definitively to distinguish between these patients and those who have diffuse brain injury and swelling on clinical examination alone.
- *Urgent CT scan*: this is the next step in most patients who have a depressed level of consciousness or focal signs (see Box 6.9). The speed with which this needs to be arranged depends upon the tempo of neurological deterioration (relative change in GCS score; ➡ Glasgow Coma Scale (GCS), p. 458) and/or the absolute level of consciousness (GCS score <8). If CT scanning is not available at your hospital, you must discuss with your regional neurosurgical centre.
- *Treatment of raised ICP* is discussed under ➡ Raised intracranial pressure, pp. 388–90; corticosteroids have no proven benefit. Discuss with your neurosurgical centre. In a rapidly deteriorating situation, it may be necessary to proceed directly to surgery. It may be decided to hyperventilate and give mannitol (1g/kg over 10–15min), while obtaining an urgent CT scan.
- *Surgery* may be indicated for extradural (➡ Extradural haemorrhage, p. 396), subdural (➡ Subdural haematoma, pp. 400–1), and possibly some intracerebral haemorrhage (➡ Intracerebral haemorrhage, pp. 398–9) and complex head wounds such as compound depressed skull fractures.
 - A general rule is that urgent evacuation is required of extradural haematomas which produce a midline shift of 5mm or more and/or 25mL in calculated volume.
 - If the extradural haemorrhage is considered too small to warrant surgery on a CT scan performed within 6h of injury, the scan should be repeated after a few hours, irrespective of whether there has been a deterioration in the patient's condition.
- *Non-operative management*: brain contusion may be evident as areas of ↑ or ↓ density, but CT is not a sensitive way to detect primary diffuse brain injury. Effacement of the cavity of the third ventricle and of the perimesencephalic cisterns suggests raised ICP, but the absence of these signs is not to be taken as an indicator of normal ICP. Many centres therefore proceed to ICP monitoring (➡ Intracranial pressure monitoring, pp. 854–5), although this is a controversial subject.

For points on patients being discharged, see Box 6.12.

Box 6.11 Indications for admission following head injury

- Confusion.
- Abnormal CT scan.
- ↓ level of consciousness (<15/15).
- Clinical or radiological evidence of skull fracture.
- Neurological signs or severe headache + vomiting.
- Difficulty in assessment (e.g. alcohol, drugs, very young/elderly).
- Concurrent medical conditions (e.g. clotting disorders, DM).
- Poor social circumstances/living alone.

NB Very brief loss of consciousness or post-traumatic amnesia is not an absolute indicator for admission, but each patient needs to be assessed on their own merits.

Box 6.12 If patients are discharged, they should be sent home with

- A responsible adult who will be with them over the next 24h.
- A head injury card which describes potential signs and symptoms (e.g. undue sleepiness, headache, vomiting, or dizziness) of delayed neurological dysfunction.

Head injury: further management

The aim of subsequent management is to minimize secondary injury to the brain other than intracranial haematomas (see Box 6.13). Management may be better undertaken at a neurosurgical centre, and if this is arranged, the guidelines in Box 6.14 should be followed for transfer.

The principles of management are:

- *Regular and frequent neurological observation:* if there is deterioration, consider whether there may be a secondary cause of brain injury contributing to this (see Box 6.13). If there are new signs of ↑ ICP, declining level of consciousness, or signs of transtentorial herniation (➡ Examination of brainstem function 3, pp. 464–5), the patient requires intubation and hyperventilation if this has not already been performed. Mannitol may be started or a repeat bolus may need to be given (➡ Measures to reduce ICP, p. 390) and repeat CT scanning may be necessary.
- *Regular monitoring of BP, blood gases, U&Es, urinary output:* pre-emptive treatment of a decline in any of these may prevent neurological deterioration. Hypotension is commonly due to sedative agents and/or hypovolaemia. But fluid therapy needs to be conducted with care because overgenerous administration may exacerbate raised ICP. Monitor CVP.
- *Prompt treatment of seizures* (➡ Status epilepticus (tonic–clonic) 1, pp. 408–9).
- *NG tube:* to administer nutrition and drugs.
- *A bowel regimen* of stool softeners might be started.

Before transfer to the neurosurgical unit

- Assess clinically for respiratory insufficiency, shock, and internal injuries.
- Perform CXR, ABG estimation, and cervical spine X-ray.
- Appropriate treatment might be to:
 - Intubate (e.g. if airway obstructed or threatened).
 - Ventilate (e.g. cyanosis, $P_aO_2 < 7.9 \text{ kPa}$, $P_aCO_2 > 5.9 \text{ kPa}$).
 - Commence IV fluids carefully.
 - Give mannitol, after consultation with neurosurgeons.
 - Apply cervical collar or cervical traction.
- The patient should be accompanied by personnel able to insert ETT, initiate or maintain ventilation, administer O_2 and fluids, and use suction.¹²

References

12. Mendelow AD, Teasdale G (1991). Decisions and guidelines for the early management of head injury patients in the UK. In: Swash M, Oxbury J, eds. *Clinical Neurology*. Churchill Livingstone, London; pp. 698–9.

Box 6.13 Causes of secondary brain injury**Systemic**

- Hypoxaemia.
- Hypotension.
- Hypercarbia.
- Severe hypocapnia.
- Pyrexia.
- Hyponatraemia.
- Anaemia.
- DIC.

Intracranial

- Haematoma (extradural, subdural, or intracerebral).
- Brain swelling/oedema.
- Raised ICP.
- Cerebral vasospasm.
- Epilepsy.
- Intracranial infection.

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Box 6.14 Indications for neurosurgical referral (and/or urgent CT head scan) following head injury

- Recent intracranial lesion seen on CT.
- Persisting coma (<9/15) after initial resuscitation.
- Confusion which persists for >4h.
- Progressive focal neurological signs.
- Seizure without full recovery.
- Depressed skull fracture.
- Definite or suspected penetrating injury.
- CSF leak or other sign of a basal skull fracture.
- Urgent CT indicated, but no local facilities available.

Source: data from *Report of the Working Party on the Management of Patients with Head Injuries* (1999). Royal College of Surgeons of England, London.

Raised intracranial pressure

Presentation

Normal ICP in adults is 0–10mmHg at rest. Treatment is required when it exceeds 15–20mmHg for >5min. Symptoms and signs suggestive of raised ICP include:

- *Headache and vomiting*: worse in mornings; exacerbated by bending.
- *Focal neurological signs*: may occur if there is an SOL and in some metabolic conditions (e.g. liver failure). But there may also be false localizing signs, e.g. cranial nerve VI palsy.
- *Seizures*: may occur with SOLs, CNS infection, or metabolic encephalopathies associated with raised ICP.
- *Papilloedema* (see Fig. 6.2): is present only if there is CSF obstruction.
- *Impaired level of consciousness*: from mild confusion to coma.
- *Signs of brain shift*:¹³ may accompany decreasing level of consciousness. They are discussed with examination of brainstem function (➡ Look for evidence of brainstem dysfunction, p. 353; ➡ Examination of brainstem function 2, p. 462).
- *Late signs*: bradycardia and hypertension.

Causes

- Head injury with intracranial haematoma/brain swelling/contusion.
- Stroke (haemorrhagic, major infarct, venous thrombosis).
- Metabolic (hepatic or renal failure, DKA, hyponatraemia, etc.).
- CNS infection (abscess, encephalitis, meningitis, malaria).
- CNS tumour.
- Status epilepticus.
- Hydrocephalus (of any cause).
- Idiopathic intracranial hypertension (IIH).

Assessment of severity

- GCS score (➡ Glasgow Coma Scale (GCS), p. 458).
- Signs of brain shift and brainstem compromise (➡ Examination of brainstem function 3, pp. 464–5).

Management

- 1 Stabilize the patient.
- 2 Consider active means of reducing the ICP.
- 3 Attempt to make a diagnosis.
- 4 Treat factors which may exacerbate raised ICP.
- 5 Observe for signs of deterioration, and attempt to reverse them.
- 6 Consider specific therapy.

What follows is the management for stabilizing a patient presenting acutely with raised ICP and may not be appropriate for many patients with a long progressive history of deterioration.¹³



Fig. 6.2 Acute papilloedema (e.g. DM; ➡ Chapter 9).

Reproduced from Easty D, et al. *Oxford Textbook of Ophthalmology*, 1999, with permission from Oxford University Press.

Stabilize the patient

- *Open the airway* by laying the patient on their side. Give O_2 . Measure ABGs. Intubation and mechanical ventilation may be necessary because of respiratory compromise. It may also be necessary to reduce ICP by hyperventilating the patient (➡ Measures to reduce ICP, p. 390) to keep P_aCO_2 between 3.3 and 4.0kPa (25–30mmHg).
- *Correct hypotension*. Volume expansion with colloids or infusions of inotropes needs to be conducted with careful and frequent monitoring of CVP and/or PAWP. In general, patients with raised ICP should be fluid-restricted to 1.5–2.0L/day. So if volume expansion is required, it should be kept to the minimum required to restore BP.
- *Treat seizures* (➡ Status epilepticus (tonic–clonic) 1, pp. 408–9).
- *Examine rapidly* for signs of head injury (➡ Head injury: presentation, p. 380). If the patient is hypotensive, examine carefully for any occult site of bleeding. If there is a rash, consider the possibility of meningococcal meningitis; take blood cultures and give antibiotics (➡ Acute bacterial meningitis: immediate management, pp. 372–3).
- Take blood for *glucose* (this may be raised in DKA or hyperosmolar non-ketotic states; it may be very low in liver failure), *U&Es* [biochemical assessment of dehydration and renal function, K^+ for susceptibility to dysrhythmia, hyponatraemia from inappropriate antidiuretic hormone (ADH), or hypernatraemia from aggressive diuretic-induced dehydration], *LFTs*, *albumin*, *clotting studies and ammonium* (to assess liver function), *FBC*, and *blood culture*.

Measures to reduce ICP

The value of ICP monitoring is a controversial subject. Irrespective of whether or not your patient's ICP is monitored, the following interventions should be considered.

- *Elevate the head of the bed* to 30° (once cervical spine injury has been excluded) to promote venous drainage.
- *Hyperventilation*, so that $P_a\text{CO}_2$ is kept between 3.7 and 3.9kPa, will promote cerebral vasoconstriction and lower cerebral blood volume—this requires intubation and paralysis. It will also lower the BP and may compromise cerebral circulation. In patients with liver failure, this is no longer recommended. Discuss with your local ITU.
- *Mannitol*: 0.5–1g/kg over 10–15min (250mL of 20% solution for an average adult) reduces ICP within 20min, and its effects should last for 2–6h. If required, further boluses of smaller doses of mannitol (0.25–0.5g/kg) may be given every few hours. U&Es and serum osmolality should be monitored, as profound diuresis may result. Serum osmolality should not be allowed to rise over 320mOsm/kg.
- *Corticosteroids* are of benefit in reducing oedema around SOLs (➡ Intracranial space-occupying lesion, pp. 394–5) but are not helpful in the treatment of stroke or head injury. Dexamethasone is given as a loading dose of 10mg IV. It may be followed by 4–6mg q6h PO/via NG tube.
- *Fluid restriction* to 1.5–2.0L/day. U&Es must be checked frequently.
- *Cooling* to 35°C reduces cerebral ischaemia.
- *Avoid/treat hyperglycaemia* because it exacerbates ischaemia.

References

13. Posner JB, Saper CB, Schiff ND, Plum F (2007). *Plum and Posner's Diagnosis of Stupor and Coma* (Contemporary Neurology Series), 4th edn. Oxford University Press, New York, NY.

Raised ICP: further management

Attempt to make a diagnosis

Often the history makes the diagnosis obvious, and usually a raised ICP is a secondary diagnosis. If a history is not available, focal neurological signs or focal seizures suggest an underlying structural cerebral lesion (although such signs may occur with hepatic or renal failure). Meningism raises the possibility of SAH or meningitis.

A CT scan should be performed in all patients suspected of having raised ICP before LP is considered.

(LP should be discussed with a senior colleague and/or neurologist.) Blood sent for analysis on admission may help to detect metabolic causes of raised ICP.

Treat factors which exacerbate raised ICP

- *Hypoxia/hypercapnia*: ABGs need to be measured regularly.
- *Inadequate analgesia, sedation, or muscle relaxation and hypertension*. NB Hypertension should not be treated aggressively. Pain, e.g. from urine retention, may be the cause. Rapid lowering of BP may lead to 'watershed'/'border-zone' cerebral infarcts.
- *Seizures* are not always easy to identify in paralysed patients.
- *Pyrexia* increases cerebral metabolism and, as a consequence, cerebral vasodilatation. It also appears to increase cerebral oedema. The cause of pyrexia should be sought, but paracetamol (given PR) and active cooling should be commenced.
- *Hypovolaemia*.
- *Hyponatraemia* is usually the result of fluid overload but may be caused by SIADH. Treat with desmopressin 1–4 micrograms IV daily (➡ Hyponatraemia: causes, pp. 372–3).¹⁴

Consider specific therapy

- Once a diagnosis is established, it may be appropriate to consider surgery in order to decompress the brain or insert a ventricular shunt to drain the CSF.
- Intracranial infections need to be treated with the most suitable antibiotics.
- Hyperglycaemia (ketotic/non-ketotic) and liver or renal failure have their own specific management (see relevant sections).
- Often, however, there may not be a specific intervention that is appropriate, e.g. contusion following head injury, and management is confined to optimizing a patient's condition while awaiting recovery.

References

14. Pickard JD, Czosnyka M. Management of raised intracranial pressure. *J Neurol Neurosurg Psychiatr* 1993;56:845–58.

Idiopathic intracranial hypertension

IIH is a syndrome of raised ICP in the absence of an intracranial mass lesion or hydrocephalus. Although rarely life-threatening, IIH can cause permanent visual loss due to optic nerve damage. This disorder affects 1 in 100,000 of the population overall, but this increases to 1:5000 obese women of child-bearing age. There is a predominance in women over men (4:1), aged 17–45 years.

Presentation

- Constant, but variable, headaches.
- Visual disturbances (including diplopia, transient visual obscurations, scotoma), nausea.
- The presence of focal neurology, including epilepsy, does *not* occur in IIH.
- Fundoscopy almost invariably shows papilloedema.

Associations

- Obesity or recent gain in weight is typical.
- Drugs (tetracycline, isotretinoin and etretinate, nalidixic acid, nitrofurantoin, and lithium).
- OCP.
- Steroid withdrawal.

Investigations

- CT or MRI head with venography are necessary to rule out venous sinus thrombosis.
- LP reveals an elevated CSF pressure ($>30\text{cm}$ is unequivocally high; $20\text{--}30\text{cmH}_2\text{O}$ is intermediate). Ensure the lateral position is used to obtain CSF (and not sat upright which would increase CSF pressure).

Treatments (seek advice)

- Losing weight.
- Identifying other causative factors such as drugs.
- Acetazolamide (maintenance dose 500mg bd).
- Surgical shunting (lumboperitoneal shunt).
- Repeated therapeutic LPs are no longer a favoured approach to treatment.

Intracranial space-occupying lesion

Presentation

- *Symptoms of raised ICP:* headache, nausea, and vomiting (➡ Raised intracranial pressure, pp. 388–90).
- *Papilloedema:* is present in the minority of cases.
- *Focal neurological symptoms and signs:* these depend upon the location of the lesion, its extent and that of surrounding cerebral oedema, and compression of long tract fibres or cranial nerves. Some lesions, particularly those in the frontal lobe, are relatively 'silent' and may produce no signs or simply a change in personality.
- *Seizures.*
- *Impaired level of consciousness:* ranging from confusion to coma.
- *Signs of brain shift* (➡ Examination of brainstem function 3, pp. 464–5) may be present.
- *Fever:* suggests an infection. There may be a recent history of earache/discharge, toothache, foreign travel, or immunocompromise.
- *Acute onset of symptoms:* suggests the possibility of a vascular event, either an infarct or bleeding into another type of lesion, e.g. tumour.

For common causes of intracranial SOLs, see Box 6.15.

Management

(See Box 6.16.) Depends upon the diagnosis. In a comatose individual with known inoperable brain metastases, it is usually not appropriate to intervene. On the other hand, if a patient presents for the first time with signs suggestive of an SOL, the diagnosis needs to be established.

- *Assess severity:*
 - If comatose, protect the airway and manage as described under ➡ Coma: immediate management, p. 350.
 - If there are signs of brain shift which suggest impending transtentorial herniation (➡ Examination of brainstem function 3, pp. 464–5), give dexamethasone [10mg IV (loading dose), followed by 4–6mg PO or NG q6h] and/or mannitol 0.5–1g/kg over 10–15min (100–250mL of 20% solution for an average adult), and hyperventilate to keep $P_a\text{CO}_2$ between 3.7 and 3.9kPa. This may be followed by smaller doses of mannitol every few hours (➡ Measures to reduce ICP, p. 390).
 - If the patient is alert and stable, it is best to await CT scan and, in the interim, make regular neurological observations.
- If the patient is *pyrexial* or the history is suggestive of *infection*, blood, sputum, and urine cultures should be sent. An urgent CT scan should be arranged for these cases; CSF analysis may be necessary, but an LP should *not* be performed before the scan or discussion with neurologists/neurosurgeons.
- If a *vascular event* is suspected, a CT scan should also be arranged urgently because decompression may be possible.
- *Seizures* should be treated. If they are recurrent, the patient may require loading with IV phenytoin. Many neurosurgeons give oral phenytoin prophylactically to patients (300mg/day; therapeutic levels are not reached for at least 5 days).
- *Steroid therapy* is given if it is thought that some of the symptoms/signs are due to tumour-related brain oedema. Give dexamethasone 10mg IV

(loading dose), followed by 4–6mg PO or NG q6h. This is a large dose of steroid (NB dexamethasone 20mg/day equivalent to prednisolone 130mg/day), and urine/blood glucose should be monitored. Duration of therapy is guided by response to the steroid and the patient's general condition.

- *Neurosurgery/radiotherapy* may be of some benefit in some individuals—discuss with your regional neurosurgical centre.

Box 6.15 Common causes of intracranial space-occupying lesions

- Cerebral tumour (primary/secondary).
- Subdural haematoma.
- Intracerebral haemorrhage.
- Tuberculoma.
- Cerebral abscess.
- Extradural haematoma.
- Subdural empyema.
- Toxoplasmosis (immunocompromised).

Box 6.16 Management key points: intracranial space-occupying lesions

- Protect the airway.
- Establish the diagnosis (urgent CT, followed by LP; if infection is suspected, send blood/urine/sputum for culture).
- If there are signs of brain shift which suggest impending transtentorial herniation (➡ Examination of brainstem function 3, p. 464–5): give 20% mannitol (100–250mL of 20% solution for an average adult) (although mannitol does not likely alter overall outcomes), and hyperventilate (requires intubation and paralysis) to keep $P_a\text{CO}_2$ between 3.7 and 3.9kPa.
- Dexamethasone (10mg IV loading dose, followed by 4–6mg qds PO/NG): reduces oedema around the SOL (monitor blood/urine glucose).
- Discuss with neurologists/neurosurgeons regarding the possibility of neurosurgery or radiotherapy.
- Treat seizures. If recurrent: load with IV phenytoin. Many neurosurgeons give oral phenytoin (300mg/day) prophylactically.
- Regular neurological observations.

Practice points

Hemisensory loss involving the trunk is likely to be due to a deep lesion involving the thalamus or deep white matter. Complete hemisensory loss may be seen in functional disorders and can be distinguished by placing a tuning fork on each side of the forehead and the sternum (1cm apart). Patients with functional disease might report that vibration is absent on the affected side (but present 1cm away on the unaffected side), which is anatomically unlikely.

Further reading

Hawkes C. Smart handles and red flags in neurological diagnosis. *Hosp Med*. 2002;63:732–42.

Extradural haemorrhage

Presentation

There are no specific diagnostic features. Consider the diagnosis in any head-injured patient who fails to improve or continues to deteriorate.

- *Head injury*: is almost invariable.
- *Skull fracture*: present in over 90% of adult cases.
- *Headache and vomiting*: may occur.
- *Impaired level of consciousness*: there may be an initial lucid interval following a head injury, but extradural haematomas may be present in patients who have been in a coma continuously after the injury. Uncommonly, if the cause is a dural venous sinus tear (rather than shearing of a meningeal artery), the lucid interval may extend for several days.
- *Seizures*.
- *Contralateral hemiparesis and extensor plantar*: may be elicited.
- *Signs of brain shift* (➡ Examination of brainstem function 3, pp. 464–5).

Causes

Common

- Head injury tearing of meningeal artery (commonly middle meningeal).

Rare

- Head injury dural sinus tear.
- Intracranial infection (sinuses, middle ear, orbit).
- Anticoagulants/blood dyscrasia.

Assessment of severity

Bilateral extensor plantars or spasticity, extensor response to painful stimuli, and coma are severe effects of an extradural haemorrhage.

Management

Depends upon the tempo of presentation. Priorities are:

- *Stabilize the patient*: protect the airway; give O₂, and support breathing and circulation. Assume C-spine injury till excluded.
- *Treat seizures* (➡ Status epilepticus (tonic–clonic) 1, pp. 408–9).
- *Urgent CT scan*:
 - Haematomas with >5mm midline shift on CT and/or >25mL calculated volume require urgent evacuation.
 - If the extradural haemorrhage is considered too small to warrant surgery on a CT scan performed within 6h of injury, the scan should be repeated after a few hours, irrespective of whether there has been a deterioration in the patient's condition.
- *Closely monitor the neurological state (including GCS score)*:
 - If the patient slips into coma and signs of tentorial herniation (➡ Examination of brainstem function 3, pp. 464–5) are progressing rapidly, give 1g/kg of 20% mannitol as a bolus and inform on-call surgeons.
 - If there is evidence of brain shift, discuss with neurosurgeons—ICP should be reduced with mannitol (0.5–1.0g/kg of 20% mannitol) and hyperventilation.
- *All patients must be discussed with neurosurgeons*: neurological impairment is potentially reversible if the extradural haematoma is treated early.

Intracerebral haemorrhage

Presentation

- Headache, nausea, and vomiting of sudden onset is common.
- Focal neurological deficit: the nature of this depends upon the location of the haemorrhage. Putaminal haemorrhages (30% of cases) or lobar bleeds (30% of cases) may lead to contralateral hemiparesis and sensory loss, visual field disturbance, dysphasia (left hemisphere), or spatial neglect (more severe with right hemisphere lesions). In other words, they may present like a middle cerebral artery (MCA) infarct (➡ Cerebral infarction syndromes, p. 424), but often there is a greater alteration in the level of consciousness. Thalamic haemorrhages (10% cases) may result in eye signs (forced downgaze, upgaze paralysis, or skew deviation), as well as contralateral sensory loss and hemiparesis. Cerebellar haemorrhage is dealt with under ➡ Cerebellar stroke, pp. 426–7 and pontine bleeds under ➡ Brainstem stroke, p. 428.
- Seizures may occur.
- Global neurological deficit with a decreasing level of consciousness progressing to coma. There may be signs of brain shift (➡ Examination of brainstem function 3, pp. 464–5).
- Hypertension.

Common predisposing factors

- Hypertension (40–50%): more commonly deep brain bleeds.
- Cerebral amyloid angiopathy: more superficial lobar bleeds.
- Anticoagulants.
- Metastatic neoplasm: bleeds may occur within the lesion.
- Drug abuse (alcohol, cocaine, pseudoephedrine, amphetamines).

Assessment of severity

A low GCS score (<9), a large-volume haematoma, and the presence of ventricular blood on the initial CT are factors that are predictive of a high mortality rate.

Management

Priorities are (see Box 6.17):

- 1 Stabilize the patient: protect the airway; give O₂ if required; support the circulation if necessary or appropriate; commence general measures for treating a comatose patient (➡ Coma: immediate management, p. 350) if necessary. If there is evidence of raised ICP, it should be reduced.
- 2 Correct bleeding tendency or effects of anticoagulants.
- 3 Make a definitive diagnosis with an urgent CT scan. Liaise with the regional neurosurgery unit early, as surgical intervention may be of benefit. Whether aggressive intervention is appropriate should be decided early.
- 4 If appropriate, intensive care/high dependency ward nursing observations are required for the drowsy or comatose patient if they are not transferred to a neurosurgical centre immediately.

- 5 Surgical decompression may be beneficial—usually for accessible bleeds within the posterior fossa (➡ Cerebellar stroke, p. 428), putamen, or thalamus.
- 6 Patients who have a seizure at the onset of the haemorrhage should receive IV anticonvulsants.
- 7 BP control: severe hypertension may worsen intracerebral haemorrhage by representing a continued force for haemorrhage and can cause hypertensive encephalopathy. Continuous IV infusion with labetalol or nicardipine may be given if the SBP is >200 mmHg. If the SBP is over 180mmHg, use either continuous or intermittent treatments. The target BP should be 160/90mmHg or slightly less. More pronounced drops in BP should be avoided (avoid lowering the SBP to <140mmHg, as this may cause ischaemia). Patients should be carefully monitored for signs of cerebral hypoperfusion induced by the fall in BP.

Box 6.17 Management key points: intracerebral haemorrhage

- Protect the airway, give O₂, support the circulation if necessary, and monitor in ITU.
- Make a definitive diagnosis with an urgent CT scan.
- Liaise with neurosurgeons regarding the possibility of surgical decompression for accessible bleeds, e.g. within the posterior fossa.
- If there is evidence of raised ICP, it should be reduced:
 - 20% mannitol: initial bolus of 1g/kg, followed by infusions of 0.25–0.5g/kg qds. The goal is to achieve plasma hyperosmolality (300–310mOsmol/kg), while maintaining an adequate plasma volume.
 - Hyperventilation: requires intubation and paralysis; discuss with local ITU.
- Correct bleeding tendency/deranged coagulation screen or effects of anticoagulants (e.g. with vitamin K, prothrombin complex concentrate, fibrinogen concentrate, platelet transfusion).
- Treat the seizure with IV anticonvulsants.
- Hypertension: if SBP >170mmHg, consider IV labetalol, nicardipine. Aim for target BP of 160/90mmHg. BP drops to SBP 140mmHg are probably safe (if initially 150–220mmHg).

Further reading

Keep RF, Hua Y, Xi G. Intracerebral haemorrhage: mechanisms of injury and therapeutic targets. *Lancet Neurol* 2012;11:720–31.

Subdural haematoma

Presentation

- This may present in one of two ways: acute or chronic. Both are usually the result of tearing of bridging veins (between the cortical surface and venous sinuses).
- Acute haemorrhage into the subdural space follows head injury and can be impossible to distinguish on clinical grounds from extradural haemorrhage (➡ Extradural haemorrhage, p. 396).
- A chronic haematoma is also preceded in most cases by head injury, but this is often so trivial that patients are unable to recollect it.
- Both types of patient may present with:
 - *Skull fracture* (more common in acute cases).
 - *Headache*.
 - *Impaired and fluctuating level of consciousness*, ranging from mild confusion through cognitive decline (e.g. impaired memory) to coma. The diagnosis should be considered in any individual, particularly the elderly, who presents with intellectual deterioration or 'dementia' of relatively recent onset.
 - *Focal neurological signs* (hemiparesis, dysphasia, hemianopia, etc.).
 - *Seizures* occur in a minority of patients.
 - *Signs of brain shift* (➡ Status epilepticus (tonic-clonic) 1, pp. 408–9) or *papilloedema*.

Common predisposing factors

- Head injury: in young or old.
- Old age: cortical atrophy stretches bridging veins.
- Long-standing alcohol abuse.
- Anticoagulant use.

Assessment of severity

The following are severe effects of a subdural haemorrhage:

- Bilateral extensor plantars or spasticity.
- Extensor response to painful stimuli.
- Coma.

Management

Depends upon the tempo of presentation.

- In suspected *chronic cases*, a CT scan is required less urgently, unless there has been an acute deterioration on a background of a steady neurological decline. Chronic haematomas become isodense with the brain and are therefore sometimes difficult to distinguish; MRI may be better.
- In *acute cases*, priorities are (see Box 6.18):
 - Protection of the airway, give O₂, and support the breathing and circulation as necessary.
 - Liaison with the neurosurgical team early.
 - Close monitoring of the neurological state (GCS score).

- Consider methods to reduce the ICP if raised; if the patient slips into coma and if signs of tentorial herniation (➡ Examination of brainstem function 3, pp. 464–5) are progressing rapidly, give 1g/kg of 20% mannitol as a bolus, inform the on-call surgeon, and arrange a very urgent CT scan.
- Treat seizures (➡ Status epilepticus (tonic–clonic) 1, pp. 408–9).

Box 6.18 Management key points: subdural haematoma

- Protection of airway, O₂.
- Liaison with the neurosurgical team early.
- Close monitoring of the neurological state (GCS score).
- If the patient deteriorates (slips into coma and signs of tentorial herniation progressing rapidly): give 1g/kg of 20% mannitol as a bolus, inform the on-call surgeon, and arrange an urgent CT scan.
- Treat seizures.

Subarachnoid haemorrhage: assessment

Presentation

- **Headache:** classically sudden and severe ('thunderclap'), radiating behind the occiput, with associated neck stiffness. Often, the time from onset to peak of headache is only a few seconds, but less dramatic presentations are common. Consider the diagnosis in any unusually severe headache, especially if the patient does not have a previous history of headaches and is >40 years. Many aneurysmal bleeds occur at/after sexual intercourse, but most coital headaches are not SAHs; 10% of patients with subarachnoid bleeds are bending or lifting heavy objects at the onset of symptoms.
- **Nausea, vomiting, dizziness:** may be transient or protracted.
- **Impaired level of consciousness:** there may be an initial transient loss of consciousness, followed by variable impairment. Patients may present in coma.
- **Early focal neurological signs:** may occur, especially if there has been a concomitant intracerebral haemorrhage. Third nerve palsy raises the possibility of a posterior communicating artery aneurysm.
- **Seizures:** are uncommon, but SAH in a person known to have fits suggests an underlying AV malformation.
- **Sentinel bleed:** between 20% and 50% of patients with documented SAH report a distinct, unusually severe headache in the days or weeks before the index bleed.¹⁶ These are often misdiagnosed as simple headaches or migraine, so a high degree of suspicion is required.
- Patients may present with secondary head injury following collapse. Blood seen on CT scanning may be attributed to trauma.

Causes

Common

- Aneurysm (70%).
- AV malformation (5%).
- No known cause in up to 20%.

Rare

- Clotting disorder/anticoagulants.
- Tumour.
- Vasculitis.
- Associated with polycystic kidney disease (berry aneurysm).

Assessment of severity (prognostic features)

- The *Hunt and Hess scale* allows grading at presentation and thereafter:
 - Grade 1: asymptomatic or minimal headache + slight neck stiffness.
 - Grade 2: moderate or severe headache with neck stiffness, but no neurological deficit other than cranial nerve palsy.
 - Grade 3: drowsiness with confusion or mild focal neurology.
 - Grade 4: stupor with moderate to severe hemiparesis or mild decerebrate rigidity.
 - Grade 5: deeply comatose with severe decerebrate rigidity.
- Prognosis is best in grade 1 (mortality <5%), worst in grade 5 (mortality 50–70%), and intermediate in between.
- Neurological deterioration following presentation has a worse prognosis. Patients should be re-graded on the Hunt and Hess scale.

Practice points

- First and worst headache in someone not prone to headaches should suggest SAH.
- Thunderclap headache may be due to a ruptured intracranial aneurysm.¹⁷
- Recurrent thunderclap headaches may herald reversible vasoconstriction syndrome (need CT or MRA).
- Patients who wake, often at the same time, with severe unilateral orbital pain lasting less than a couple of hours will usually have cluster headache. Mostly middle-aged ♂.¹⁷

References

16. Edlow JA, Caplan LR. Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. *N Engl J Med* 2000;**342**:29–35.
17. Hawkes C. Smart handles and red flags in neurological diagnosis. *Hosp Med* 2002;**63**:732–42.

Subarachnoid haemorrhage: immediate management

Confirm the diagnosis

- *Urgent HRCT scanning* is required. This will clinch the diagnosis in 95% of patients scanned within 24h. Furthermore, it gives valuable information regarding a possible location of the aneurysm and may even demonstrate AV malformation. It may also display concomitant intracerebral and/or intraventricular bleeds.
- *LP* is *not* usually required, unless the CT scan is normal but the history is highly suggestive. It is important to examine the CSF for blood under these circumstances; the presenting event may be a 'warning leak'. Blood in the CSF may result from a traumatic tap. If this is the case, there may be diminishing numbers of red cells in each successive tube of CSF (although this is not always reliable). If the blood has been present for >6h, the supernatant should be xanthochromic after centrifugation.
- Once the diagnosis is confirmed, discuss with regional neurosurgeons.
- Transfer grade 1 and 2 patients as soon as possible. Surgery will prevent re-bleeding, and although the optimal time for operation is debated (2 days versus 7–10 days post-bleed), outcome is probably improved by early transfer.
- Surgery on poor-prognosis patients is unrewarding; they are usually managed conservatively. However, suitability for surgery should be reassessed if their condition improves.

Stabilize the patient

(See Box 6.19.)

- *Protect the airway* by laying the drowsy patient in the recovery position. Give O₂.
- Consider *measures to reduce ICP* if signs suggest it is raised (➡ Raised intracranial pressure, pp. 388–90), but avoid dehydration and hypotension.
- *Treat seizures* with usual drugs (➡ Status epilepticus (tonic–clonic) 1, pp. 408–9), but beware of over-sedation and hypotension.
- *Correct hypotension*, if necessary, with colloid or inotropes.
- *To avoid hypertension*, the patient should be nursed in a quiet room; sedatives may be required, and stool softeners should be given to avoid straining. Once the diagnosis is established, nimodipine is usually given to reduce vasospasm; it helps also to reduce BP.
- *ECG monitoring and treat dysrhythmias* if they compromise BP or threaten thromboembolism. Rarely, SAH is associated with (neurogenic) pulmonary oedema.
- Take blood for *clotting screen* (if bleeding diathesis suspected) and *U&Es* (biochemical assessment of dehydration, K⁺ for susceptibility to dysrhythmia, hyponatraemia from inappropriate ADH or from aggressive diuretic-induced dehydration).

Box 6.19 Management key points: subarachnoid haemorrhage

- Protect the airway (lie the patient in the recovery position). Give O₂.
- Correct hypotension (and electrolyte disturbances).
- Treat seizures with usual drugs (but beware of over-sedation and hypotension).
- Discuss with regional neurosurgeons when the diagnosis is confirmed (on urgent CT; LP for ? xanthochromia if CT is normal but history is highly suggestive (if the blood has been present for >6h).
- Nimodipine 60mg PO 4-hourly for up to 21 days.
- Appropriate analgesia (codeine phosphate) and antiemetics for awake patients.
- Regular neurological observations to detect a deterioration (? secondary to cerebral ischaemia, re-bleeding, or acute hydrocephalus): CT scan should be performed.

Further reading

Burrows AM, Korumilli R, Lanzino G. How we do it: acute management of subarachnoid hemorrhage. *Neurol Res* 2013;35:111–16.

Subarachnoid haemorrhage: further management

Specific therapies

- *Nimodipine* is a calcium channel blocker which works preferentially on cerebral vessels to reduce vasospasm (and consequent cerebral ischaemia).¹⁸ It has been shown to reduce morbidity and mortality following SAH. Give 60mg PO (or in the comatose patient) every 4h; IV therapy is costly and requires central venous access.
- *Antifibrinolytics* were introduced to prevent lysis of clot and re-bleeding. They have been associated with thrombotic complications and are not advised at present.
- Appropriate analgesia (codeine phosphate 30–60mg every 4–6h) and antiemetics should be given for awake patients.¹⁹

Observe for deterioration; attempt to reverse it

Neurological observations should be performed regularly. If there is a deterioration, e.g. lowering of the level of consciousness, a CT scan should be performed. There are several possible mechanisms for deterioration:

- *Cerebral ischaemia* is usually insidious and multifocal. It may give rise to focal and/or global neurological deterioration. Volume expansion with colloid or induced hypertension with inotropes have been attempted, but these procedures have not been properly studied.
- *Re-bleeding* may be immediately fatal or lead to apnoea. It is reported that assisted ventilation for 1h may be all that is necessary for spontaneous breathing to return to the majority of apnoeic individuals.²⁰ Patients who re-bleed are at high risk of further bleeding and should be considered for emergency aneurysm clipping.
- *Acute hydrocephalus* may be treated with ventricular drainage. This can lead to dramatic improvement in the patient's condition.

Refer for definitive treatment

Unless the patient has a poor prognosis (see Hunt & Hess Scale in  Subarachnoid haemorrhage: assessment, p. 402), they should be cared for at a neurosurgical centre. The complications listed here should be managed by clinicians experienced in treating them.

References

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- Kirkpatrick PJ. Subarachnoid haemorrhage and intracranial aneurysms: what neurologists need to know. *J Neurol Neurosurg Psychiatr* 2002;73(Suppl 1):i28–33.
- van Gijn J. Subarachnoid haemorrhage. *Lancet* 1992;339:653–5.

Status epilepticus (tonic–clonic) 1

Presentation

Generalized tonic–clonic status epilepticus²¹ is either continuous tonic–clonic convulsions (30min or longer, but treatment should usually begin well before this) or convulsions so frequent that each attack begins before the previous post-ictal period ends.

Causes

- Cerebral tumour (primary/secondary).
- Intracranial infection.
- Hypoglycaemia.
- Head injury.
- Electrolyte disturbance (low Na^+ , Ca^{2+} , or Mg^{2+}).
- Drug OD (e.g. tricyclics).
- Drug withdrawal (e.g. alcohol).
- Hypoxia (e.g. post-cardiac arrest).
- Sequela of stroke.
- Anti-epileptic non-compliance/withdrawal.

NB Most episodes of status do not occur in known epileptic patients. Most patients will thus need brain imaging once stabilized and safe to do so.

Management

(See Box 6.20.)

Priorities

- 1 Stabilize the patient. Give O_2 .
- 2 Anti-epileptic drug therapy.
- 3 Attempt to identify the aetiology.
- 4 Identify and treat medical complications.
- 5 Initiate long-term maintenance therapy, if appropriate.

Stabilize the patient

- *Open the airway* by laying the patient on the side in a semi-prone position, with the head slightly lower to prevent aspiration. Usually an oral airway will suffice and ET intubation is rarely necessary.
- Give O_2 .
- *Correct hypotension* with colloid, if necessary. Obtain an ECG if the patient is hypotensive. CVP monitoring may be necessary.
- Take blood for *U&Es, glucose, Ca^{2+} , Mg^{2+} , liver enzymes, and FBC*; if relevant, blood should also be sent for *toxicology screen* (if drug OD or abuse suspected) and *anticonvulsant levels*.
- *Thiamine 250mg IV* should be given if alcoholism or other malnourished states appear likely.
- If hypoglycaemia is suspected, *50mL of 50% glucose* should be administered IV. Because glucose increases the risk of WE, thiamine 1–2mg/kg IV should be administered beforehand in any patient suspected of alcohol excess.

Anti-epileptic drug therapy

- A number of agents may be used:²²
 - Benzodiazepines (diazepam, lorazepam).
 - Phenytoin.
 - Fosphenytoin.
 - Miscellaneous (general anaesthesia).

- *Lorazepam* 0.07mg/kg IV (usually 4mg bolus, which may be repeated once after 10min). Because lorazepam does not accumulate in lipid stores and has strong cerebral binding and a long duration of action, it has distinct advantages over diazepam in early status epilepticus.
- Alternatively, *diazepam* 10–20mg IV or PR, repeated once 15min later if necessary. IV injection should not exceed 2–5mg/min. Diazepam is rapidly redistributed and therefore has a short duration of action. With repeated dosing, however, as peripheral lipid compartments become saturated, there is less redistribution and blood diazepam levels increase. When this happens, there is a risk of sudden central nervous and respiratory depression, as well as cardiorespiratory collapse.
- With benzodiazepine, start an infusion of *phenytoin* 15–18mg/kg at a rate of 50mg/min (e.g. 1g over 20min). NB 5% glucose is not compatible with phenytoin. The patient should have ECG monitoring, because phenytoin may induce cardiac dysrhythmias; pulse, BP, and RR should also be monitored. IV phenytoin is relatively contraindicated in patients with known heart disease, particularly those with conduction abnormalities.
- An alternative is *fosphenytoin* given as an infusion of 15mg PE (phenytoin equivalents) at a rate of 100mg PE/min (i.e. about 1000mg PE in an average adult over 10min).
- In refractory status (seizures continuing for 60–90min after initial therapy), the patient should be transferred to intensive care.
 - General anaesthesia with either *propofol* or *thiopental* should be administered.
 - *Treat raised ICP* (➡ Raised intracranial pressure, pp. 388–90).
 - *EEG monitoring* should be commenced, if available.
 - The anaesthetic agent should be continued for 12–24h after the last clinical or electrographic seizure; the dose should then be tapered down.

If treatment is failing to control seizures, consider whether

- Initial drug dose is adequate.
- Maintenance therapy has been started and is adequate.
- The underlying cause of status epilepticus has been correctly identified.
- Complications of status adequately treated (➡ Status epilepticus (tonic–clonic) 2, p. 410; see Box 6.20).
- Coexisting conditions have been identified (e.g. hepatic failure).
- Epileptic patient's usual medications are being administered.
- There has been a misdiagnosis: is this 'pseudo-status'?

References

21. Hocker S, Wijdicks EF, Rabinstein AA. Refractory status epilepticus: new insights in presentation, treatment, and outcome. *Neurol Res* 2013;35:163–8.
22. Shorvon SD. The management of status epilepticus. *J Neurol Neurosurg Psychiatr* 2001;70 (Suppl 2):ii22–7.

Status epilepticus (tonic–clonic) 2

Attempt to identify the aetiology

- A history of previous anticonvulsant use, drug abuse/withdrawal (including alcohol), DM, trauma, or recent surgery (e.g. hypocalcaemia post-thyroid or parathyroid surgery) is obviously helpful.
- Examine the patient for signs of head trauma, meningism, focal neurological deficit (the seizures may also have some focal characteristics), needle tracks, or insulin injection sites.
- Consider an urgent CT scan if head injury may be a precipitant; an LP may be necessary if CSF infection is likely.
- Although hypoglycaemia and hypocalcaemia should be corrected promptly, hyponatraemia should be reversed cautiously because of the possibility of precipitating pontine myelinosis.

See Box 6.20 for key points in management.

Identify and treat medical complications of status

Treatment is required for:

- | | |
|--|-------------------------------|
| • Hypoxia. | • Rhabdomyolysis. |
| • Lactic acidosis. | • Hypo-/hypertension. |
| • Hypoglycaemia. | • Raised ICP. |
| • Dysrhythmias. | • Hyperpyrexia. |
| • Electrolyte disturbance
(especially hyponatraemia,
hypo-/hyperkalaemia). | • Pulmonary oedema.
• DIC. |

These complications are managed as in other contexts.

Initiate long-term therapy (if appropriate)

Some disorders, e.g. hypoglycaemia in a diabetic taking insulin, do not require long-term anticonvulsant therapy, but rather correction of the underlying problem. Other conditions may need anticonvulsant treatment for a short while, e.g. alcohol withdrawal, posterior reversible encephalopathy syndrome, or indefinitely, e.g. repeated status epilepticus in multi-infarct dementia.

- *Sodium valproate* is a reasonable first-choice treatment but avoid in women of child-bearing age.²³ Initially, sodium valproate should be given 400–600mg/day PO in divided doses (IV therapy can also be given). It should be ↑ by 200mg/day at 3- to 6-day intervals; the maintenance dose is 20–30mg/kg/day (usual adult dose is 1–2g/day). Alternative monotherapies include lamotrigine and carbamazepine. Levetiracetam is being increasingly used in this setting, as it can be rapidly titrated and has a low interaction with other medications and does not require monitoring. *Phenytoin* may be continued after IV loading at daily dosages of 5mg/kg (about 300mg for an average adult) either PO or via an NG tube or slow IVI. Dosage should be guided by phenytoin level measurements. Plasma concentration for optimum response is 10–20mg/L (40–80micromol/L). Phenytoin is disadvantageous, because it requires monitoring and its side effects.
- *Driving advice* (see Box 6.21).

Box 6.20 Management key points: status epilepticus

- Open the airway (lie the patient on the side in a semi-prone position, with the head slightly lower to prevent aspiration; oral airway, if necessary). Give O_2 .
- Correct hypoglycaemia (50mL of 50% glucose; give 250mg IV thiamine before glucose if alcoholism or malnourishment is likely) and hypotension.
- Lorazepam (4mg IV bolus, may be repeated once after 10min) or diazepam 10–20mg IV or PR (may be repeated once 15min).
- In addition to lorazepam, start phenytoin at 15mg/kg at a rate of 50mg/min (e.g. 1g over 20min), with ECG monitoring.
- In refractory status (seizures continuing for 60–90min after initial therapy): general anaesthesia with either propofol or thiopentone, with EEG monitoring. Continue the anaesthetic agent for 12–24h after the last clinical or electrographic seizure; the dose should then be tapered down.
- Attempt to identify the aetiology: send blood for U&Es, glucose, Ca^{2+} , Mg^{2+} , liver enzymes, FBC (including platelets), anticonvulsant levels, and, if relevant, toxicology screen (if drug OD or abuse suspected). Is there a new infection (e.g. respiratory tract or urinary tract)? Establish compliance with medications. Any new medications taken or dose alterations made?

Box 6.21 Driving advice

In the UK, patients should inform the Driver and Vehicle Licensing Agency (Swansea). Driving licences are revoked until the patient has been free of daytime seizures for 1 year, treated or untreated. Drivers of large-goods or passenger-carrying vehicles usually have those licences revoked permanently.

For current medical standards of fitness to drive, go to  http://www.dvla.gov.uk/at_a_glance/content.htm

References

23. Smith D, Chadwick D. The management of epilepsy. *J Neurol Neurosurg Psychiatr* 2001;**70**(Suppl 2):ii15–21.

Stroke: overview

Presentation

- Sudden-onset focal deficit of cerebral function is the most common presentation.
- Alternative presentations can include apparent confusion (e.g. due to dysphasia or visuospatial impairment), seizures, declining levels of consciousness or global loss of brain function, and coma.
- If symptoms last for >24h (or lead to death) and there is no apparent cause other than a vascular event, the diagnosis is most likely to be a stroke. If the symptoms last <24h and, after adequate investigation, are presumed to be due to thrombosis or embolism, the diagnosis is a TIA. TIAs tend, however, to last from minutes to 1–2h.

Causes

- Thrombosis or embolism causing cerebral infarction (80% cases).
- Primary intracerebral haemorrhage (15% cases).
- SAH (5% cases).
- Cerebral venous thrombosis (1%).

Risk factors

See Box 6.22.

Differential diagnosis

Many conditions may masquerade as a stroke:

- | | |
|---|----------------------------------|
| • Cerebral tumour (primary or secondary). | • Functional (psychogenic). |
| • Brain abscess. | • Subdural haematoma. |
| • Demyelination. | • Todd's paresis (post-seizure). |
| • Focal migraine. | • Hypoglycaemic attack. |
| | • Encephalitis. |

An alternative diagnosis to stroke is more likely in:

- | | |
|---|--|
| • Patients <45 years. | • Absence of risk factors. |
| • Presence of seizures. | • Fluctuating levels of consciousness. |
| • Presence of papilloedema. | • Pyrexia (at presentation). |
| • Prolonged and/or discontinuous evolution of symptoms. | |

In general, a stroke commences suddenly and the deficit is at its peak and established within 24h. If the evolution of symptoms is longer or progresses in a stuttering way over days or weeks, an SOL must be suspected. If there is a variable depression of consciousness, the diagnosis of a subdural haematoma should be entertained, and pyrexia at presentation should alert one to the possibility of a cerebral abscess.

Seizures occur in 5–10% of strokes at their onset, although they are frequent sequelae. Papilloedema would be extremely unusual in arterial strokes but may occur in cerebral venous sinus thrombosis. Consider this diagnosis, particularly in patients who may have become dehydrated and young women (particularly during the puerperium) with headache and seizures $\pm$ focal signs.

Dissection of the internal carotid or vertebral arteries should always be considered, particularly in younger patients who may have experienced only mild neck trauma. Often, however, there may be no clear history of preceding trauma. Carotid dissection may be accompanied by Horner's syndrome; vertebral dissection presents with symptoms associated with brainstem stroke.

Box 6.22 Risk factors for stroke

Global

- Increasing age.
- Hypertension.
- DM.
- Family history.
- Hyperlipidaemia.
- Homocysteinaemia.

Lifestyle

- Drug abuse (cocaine).
- Smoking.
- OCP.
- Hormone replacement therapy (HRT).
- Diving (Caisson's disease).
- Neck trauma/manipulation.

Cerebral

- Cerebrovascular disease.
- Berry aneurysms.
- Cerebral amyloid.
- Cerebral AV malformation.

Cardiac

- AF.
- MI.
- LV aneurysm.
- IHD.
- Cyanotic heart disease.
- PFO.
- Endocarditis.

Peripheral vascular

- Carotid stenosis.
- Pulmonary AV malformations.
- Ehlers–Danlos.
- Type IV (carotid dissection).

Haematological

- Hypercoagulable states.
- Polycythaemia.
- Sickle-cell disease.
- Warfarin (haemorrhage).
- Thrombolysis.

Practice points

Hemisensory loss involving the trunk is likely to be due to a deep lesion involving the thalamus or deep white matter. Complete hemisensory loss may be seen in functional disorders and can be distinguished by placing a tuning fork on each side of the forehead and the sternum (1cm apart). Patients with functional disease might report that vibration is absent on the affected side (but present 1cm away on the unaffected side), which is anatomically unlikely.

Stroke: haemorrhage or infarct?

Intracerebral haemorrhage can have an apoplectic onset with a combination of headache, neck stiffness, vomiting, and loss of consciousness of acute onset. Conscious level can be depressed for >24h; there may be bilateral extensor plantar responses, and the BP is more likely to be raised 24h after admission. But although features such as these have been integrated into scoring systems, it is not possible with certainty to differentiate an ischaemic from a haemorrhagic stroke on clinical grounds alone. A CT scan is required.

When to scan?

All patients suspected of having a stroke should be scanned as soon as possible, at least within 24h of onset. If onset within a few hours, imaging should occur immediately. CT is the investigation of choice in the majority of cases because it is better at detecting haemorrhage in the early stages, compared with standard MRI sequences, allowing triage for thrombolytic treatment, and is more readily available as an imaging modality. After the first 24h, and in cases where the stroke is suspected to involve the brainstem or cerebellum, MRI is superior. Where the CT scan is normal, diffusion-weighted MRI may reveal areas of cerebral ischaemia or infarction.

Urgent CT should be performed in the presence of

- Depressed level of consciousness.
- History of anticoagulant treatment or known coagulopathy.
- No available history.
- Features suggesting an alternative diagnosis requiring immediate action, in particular:
 - SAH (severe headache, depressed level of consciousness, neck stiffness).
 - Subdural haemorrhage (headache, history of minor trauma, progressive or fluctuating signs and symptoms).
 - SOL (depressed level of consciousness, progressive signs, papilloedema).
 - Cerebral infection (headache, fever, neck stiffness, cranial nerve palsies).
- Indications for thrombolysis (see Box 6.23) or early anticoagulation.

Brain imaging should always be undertaken before anticoagulant treatment is started.

Stroke: thrombolysis/thrombectomy

(See Boxes 6.23 and 6.24.)

Box 6.23 Thrombolysis in acute ischaemic stroke

- Availability of thrombolysis in the UK has been consolidated to a few major centres (hyperacute stroke units) in some regions.
- Use of thrombolysis for acute ischaemic stroke requires coordination of emergency services, stroke neurology, intensive care, and radiology services.
- Early identification of patients who might benefit from thrombolysis is crucial. Patients should have a neurologic deficit that is sufficiently significant to warrant exposure to the risks of thrombolysis.
- Urgent CT or MRI is mandatory to exclude brain haemorrhage.
- IV alteplase may be used in acute ischaemic stroke (MCA or basilar occlusion), provided that treatment is initiated within 4.5h of clearly defined symptom onset.
- BP must be <185/110mmHg prior to thrombolysis. However, avoid excessive BP-lowering which may worsen blood flow and cerebral ischemia.
- Inclusion criteria:
 - Clinical diagnosis of acute ischaemic stroke, with the onset of symptoms within 4.5h of commencement of thrombolysis and with a measurable neurological deficit.
- Exclusion criteria:
 - History:
 - MI, stroke, or head trauma within the previous 3 months.
 - LP or arterial puncture at a non-compressible site within previous 7 days.
 - Major operation within previous 14 days.
 - GI or genitourinary haemorrhage within previous 21 days.
 - Any previous history of intracranial bleed.
 - Active haemorrhage or acute trauma/fracture.
 - Rapidly improving stroke symptoms.
 - Seizure at the onset of stroke with post-ictal neurological impairments.
 - History suggestive of SAH.
 - Pregnancy or breastfeeding.
 - Examination:
 - Only minor and isolated neurological signs.
 - Persistent SBP >185mmHg, DBP >110mmHg, or requiring aggressive therapy to control BP.
 - Blood tests:
 - Platelet <100 000/mm³.
 - Serum glucose <2.8mmol/L or >22.2mmol/L.
 - INR >1.7 if on warfarin; elevated APTT if on heparin.
 - Head CT: evidence of haemorrhage or signs of major early infarct, e.g. diffuse swelling of the affected hemisphere, parenchymal hypodensity or effacement of >1/3 of the MCA territory.

Box 6.23 (Contd.)

- Eligibility criteria for treatment in the 3–4.5h after an acute stroke are similar to those for treatment at earlier time periods, with any one of the following additional exclusion criteria:
 - Patients older than 80 years.
 - All patients taking oral anticoagulants are excluded, regardless of the INR.
 - Patients with baseline National Institutes of Health Stroke Scale (NIHSS) score >25.
 - Patients with a history of stroke and DM.

Source: data from Report of the Quality Standards Subcommittee of the American Academy of Neurology (1996). 'Practice advisory: thrombolytic therapy for acute ischemic stroke – summary statement.' *Neurology* 47: 835–9; and Adams HP, et al. (2003). 'Guidelines for the early management of patients with ischemic stroke: A scientific statement from the Stroke Council of the American Stroke Association.' *Stroke* 34: 1056–83.

Box 6.24 Thrombectomy in acute ischaemic stroke

- A significant development in the treatment of acute ischaemic stroke.
- Availability of thrombectomy is currently limited in the UK and is being consolidated to a few major centres in some regions.
- Eligibility criteria include:
 - NIHSS >5 or functionally disabling stroke (e.g. aphasia).
 - Large-vessel anterior circulation occlusion (carotid artery, middle cerebral artery, M1).
 - Lack of extensive early ischaemic change [e.g. Alberta Stroke Programme Early CT score (ASPECTS) >5 on plain CT—clear benefit].
 - Good pre-stroke functional status (age >80 NOT a contraindication).
 - Within 6h of stroke (but perfusion mismatch imaging may allow a delayed approach).
 - Preceding thrombolysis can occur.

Stroke: other investigations

Apart from a CT scan, there are some basic tests that most patients suspected of having a stroke should have:

- *FBC*: to detect polycythaemia, thrombocythaemia, or thrombocytopenia.
- *ESR and CRP*: to screen for vasculitis, endocarditis, hyperviscosity.
- *Electrolytes and Ca^{2+}* : a neurological defect may be non-vascular and caused by hyponatraemia, hypercalcaemia, or renal failure.
- *Glucose*: to exclude hypoglycaemia and non-ketotic hyperglycaemia (which can mimic stroke) and DM (a risk factor).
- *Cholesterol*.
- *PT/INR*: if the patient is taking warfarin.
- *ECG*: to determine cardiac rhythm and exclude acute MI.
- *Carotid Doppler ultrasound*: to exclude high-grade (>70%) stenosis or dissection. This should be performed in patients who would be suitable for carotid endarterectomy or angioplasty. A bruit need not be present!
- *Cardiac echocardiography*: may demonstrate the presence of valvular disease or intracardiac clot, or may detect some rare causes of stroke such as atrial myxoma or PFO. The yield of a clinically meaningful abnormality on standard TTE is low in unselected ischaemic stroke.

Young patients, or those without common risk factors for stroke (see Box 6.22), should be investigated further. Possible tests include:

- *Serum protein, electrophoresis, viscosity*: in hyperviscosity syndromes, the ESR is usually raised, but not always.
- *Autoantibody screen*: particularly for SLE).
- *Haemostatic profile*: in haemorrhagic stroke not apparently secondary to hypertension, measurement of PT, APTT, bleeding time, and fibrin degradation products may be indicated. In cerebral infarcts, blood should be taken for proteins S and C, antithrombin III, and anticardiolipin antibodies. APTT may be prolonged in anticardiolipin syndrome. Consider testing for sickle-cell in black patients. The factor V Leiden mutation may be an important risk factor for the development of venous thrombosis.
- *Toxicology screen*: on admission sample if drug abuse (e.g. cocaine, pseudoephedrine, or amphetamines) suspected.
- *Urine tests*: may detect homocystinuria (without other clinical manifestations) or porphyria. If BP is labile, consider pheochromocytoma and measure urinary catecholamines.
- *CSF analysis*: may be necessary if the diagnosis of stroke is not well established, e.g. normal CT scan and no risk factors.
- *Cerebral angiography*: is also reserved for cases where the diagnosis is not well established and in those in whom cerebral vasculitis or malformation is suspected.
- *MRI*: is more sensitive at detecting small infarcts, cerebral venous thrombosis, and lesions in the posterior fossa. In expert hands, contrast-enhanced MRA may be comparable to conventional angiography.

Stroke: management

(See Box 6.25.)

Box 6.25 Key points: assessment and management of acute ischaemic stroke

Assessment

- Exclude hypoglycaemia.
- Brain imaging should be undertaken as soon as possible, at most within 24h of onset.
- It should be undertaken as a matter of urgency in patients with:
 - Known bleeding tendency or those on anticoagulants.
 - ↓ level of consciousness.
 - Unexplained progressive or fluctuating symptoms.
 - Papilloedema, neck stiffness, or fever.
 - Severe headache at onset.
 - Indications for thrombolysis.
- Thrombolysis if indicated (<4.5h from symptom onset) (see Box 6.23).
- Assess swallowing before giving oral foods, fluid, or oral medication on admission. If impaired: specialist assessment within 24–72h of admission.
- Screen for malnutrition.

Acute interventions

- Admit to a specialist acute stroke unit for specialist monitoring and treatment.
- Give aspirin (300mg) PO or PR as soon as possible after a primary haemorrhage has been excluded.
- Control hydration, temperature (<37.2°C), and BP; maintain O₂ (>95%) and blood glucose (4–11mmol/L).
- If surgical referral for decompressive craniectomy is indicated*: refer immediately.
- Maintain adequate nutrition (initiate IV/NG tube feeding if the patient is unable to take adequate nutrition and fluids PO).
- Patients should be mobilized as soon as possible.

Secondary prevention

- Give appropriate advice on lifestyle factors.
- Hypertension persisting for >2 weeks should be treated (target: <140/85mmHg; diabetics <130/80mmHg). Use a thiazide diuretic (e.g. bendroflumethiazide or indapamide) or an ACEI (e.g. perindopril or ramipril), or preferably a combination of both, unless there are contraindications.
- Patients who are not on anticoagulation should be taking clopidogrel 75mg daily after the first 2 weeks of high-dose aspirin.
- Start anticoagulation in patients with AF (persistent or paroxysmal), unless contraindicated.

Box 6.25 (*Contd.*)

- Anticoagulants should not be started until brain imaging has excluded a haemorrhage and not until 14 days have passed from the onset of an ischaemic stroke.
- Treatment with a statin (e.g. 40mg simvastatin) if total cholesterol >3.5mmol/L, unless contraindicated.
- Any patient with a carotid artery territory stroke and carotid artery stenosis of 70–99%, without severe disability, should be considered for carotid endarterectomy.

* Indications for decompressive craniectomy: clinical deficits suggestive of an MCA territory infarction with a score on the NIHSS of >15; decrease in the level of consciousness to a score of ≥ 1 on item 1a of the NIHSS; signs on CT of an infarct of at least 50% of the MCA territory, or an infarct volume $>143\text{cm}^2$, as shown on MRI with diffusion-weighted imaging. There are recent trial data to suggest benefit in those over 60 years, as well as those under 60 years.

Stroke: complications

Cerebral complications

Further neurological deterioration may be caused by the following:

- *Transtentorial herniation* (➡ Examination of brainstem function 3, pp. 464–5) is the most common cause of death within the first week and carries a mortality of 80%. It is due to raised ICP (➡ Raised intracranial pressure, pp. 388–90) secondary to cerebral oedema and, in ischaemic stroke, is most common after large MCA infarcts. Corticosteroids do not improve outcome; mannitol and hyperventilation may be useful temporary measures (➡ Raised intracranial pressure, pp. 388–90); surgical decompression may be indicated in large haemorrhages, particularly cerebellar ones.
- *Haemorrhagic transformation* occurs in 30% of ischaemic strokes (and up to 70% of cardioembolic strokes), usually 12h to 4 days after the event. Neurological deterioration is usually due to a mass effect.
- *Acute hydrocephalus* due to compression of the aqueduct of Sylvius by oedema or blood may occur. Ventricular shunting may be of value.
- *Seizures* complicate 10% of infarcts and are most common in large, haemorrhagic, and cortical strokes. They usually respond to monotherapy (e.g. phenytoin).
- *SIADH* occurs in 10–15% of strokes. It may initiate or worsen cerebral oedema and is treated by fluid restriction.
- *Depression* occurs in 50% and may require therapy if it persists.²⁴

Systemic complications

- *Aspiration* is common. Dysphagia occurs in at least half of all cases of stroke; the incidence is higher in those with brainstem involvement or pre-existing cerebrovascular disease. It is often undetected at bedside and usually leads to aspiration. Testing the gag reflex is not a sufficient assessment; swallowing must be observed, and if there is any suspicion, video-fluoroscopy may be used. Patients should generally be fed upright.²⁵
- *Infection* is a common cause of death following a stroke. Pneumonia (including aspiration) and UTIs are the usual problems.
- *Fever* usually occurs as a result of infection or DVT. Occasionally, it is a direct result of cerebral damage.
- *VTE*: the incidence of DVT following a stroke is comparable to that following hip or knee arthroplasty. PE accounts for up to 25% of early deaths following a stroke. Use of prophylactic anticoagulants reduces the incidence of VTE, but it is associated with an ↑ risk of haemorrhagic transformation which may outweigh any benefit. Many physicians use prophylactic LMWH, although the Royal College of Physicians (RCP) guidelines recommend compression stockings only. In the absence of intracranial haemorrhage, subclinical or overt proximal DVT should be treated with standard therapy. Below-knee DVT should be managed with compression stockings and serial USS monitoring for evidence of proximal extension.
- *Pressure sores* occur easily, unless patients are regularly turned.

References

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25. Perry L, Love CP. Screening for dysphagia and aspiration in acute stroke: a systematic review. *Dysphagia* 2001 Winter;**16**:7–18.

Stroke: secondary prevention

- *Attempt to modify 'risk factors'* (see Box 6.22): target BP should be below 140/85mmHg (lower in diabetics). There is little to choose between the different classes of drugs—all reduce the risk of further events. Consider statins, especially in those with coexisting IHD.²⁶
- *Antiplatelet drugs*: aspirin reduces the recurrence of stroke and death from other causes. In the absence of absolute contraindications, aspirin (300mg initially for 2 weeks and clopidogrel 75mg od thereafter) should be given immediately after the onset of stroke symptoms once haemorrhage has been ruled out. Patients should be treated chronically with clopidogrel 75mg daily.
- *Anticoagulants*: to prevent recurrence of ischaemic stroke, warfarin is superior to aspirin in valvular, non-valvular, and paroxysmal AF, but it is associated with ↑ risk of major bleeding. The balance of benefit may depend on the patient group but generally favours warfarin, particularly in valvular AF. Aim for an INR of 2–3, provided there are no contraindications and regular checks of INR are practicable. Current practice is to delay warfarinization for 2 weeks after the event, and to repeat the scan where the infarct is very large or where there is clinical suspicion of haemorrhagic transformation. There is no place for either UFH or LMWH. In such cases, it is best to discuss the management with a senior colleague. IV heparinization should be commenced immediately in patients with proven cerebral venous thrombosis (regardless of the presence of haemorrhagic change on CT), and many neurologists would also do the same for carotid/vertebral dissection.
- *Carotid endarterectomy*: should be considered in all patients with >70% of ipsilesional stenosis. The operation has an appreciable morbidity (including further stroke) and mortality but appears to improve overall prognosis in selected patients. In centres with experience of the procedure, carotid angioplasty may be an alternative, particularly in patients who are considered poor surgical candidates.
- *PFO*: some advocate closure using an endovascular device, but there is only anecdotal evidence of its effectiveness. Current prospective evidence suggests that stroke patients with PFOs treated with aspirin or warfarin only do not have an ↑ risk of recurrent stroke or death, compared with controls.²⁷
- *HRT and the OCP*: combined HRT increases the risk of ischaemic stroke and should be stopped. The combined, but not the progestogen-only, OCP also appears to be associated with an ↑ risk of stroke. Switch to a progestogen-only formulation or alternative forms of contraception.

References

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27. Homma S, Sacco RL, Di Tullio MR, et al.; PFO in Cryptogenic Stroke Study (PICSS) Investigators. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation* 2002;105:2625–31.

Cerebral infarction syndromes

Anterior (carotid territory) circulation

Middle cerebral artery syndrome

- Total occlusion of the MCA (usually embolic) leads to contralateral hemiplegia, hemianaesthesia, homonymous hemianopia, and deviation of the head and eyes towards the side of the lesion.
- Left-sided lesions cause global dysphasia; right-sided ones are more likely to cause unilateral neglect of contralateral space.
- Branch occlusions of the MCA are more common and cause incomplete syndromes, e.g. occlusion of upper branches cause Broca's ('non-fluent' or expressive) dysphasia and contralateral lower face and arm weakness; lower branch occlusion, on the other hand, may cause Wernicke's ('fluent' or receptive) dysphasia.

Anterior cerebral artery syndrome

Occlusion of this artery (often embolic) can lead to paralysis of the contralateral leg, gegenhalten rigidity, perseveration, alien limb syndrome, grasp reflex in the opposite hand, and urinary incontinence.

Posterior circulation

Posterior cerebral artery syndrome

Occlusion by thrombus or embolus may lead to combinations of contralateral homonymous hemianopia/upper quadrantanopia, mild contralateral hemiparesis and/or hemisensory loss, dyslexia, and memory impairment.

Lacunar infarction

Infarcts in small penetrating vessels, often the consequence of hypertension, cause a number of syndromes: pure motor stroke or pure sensory stroke, sensorimotor stroke, ataxic hemiparesis (combined cerebellar and pyramidal signs in the same limb), and dysarthria clumsy-hand syndrome.

Prognostic significance

Prognosis based on these criteria alone are no longer used in routine practice.

Brainstem stroke

Presentation

Sudden onset of:

- *Headache, nausea, vomiting, vertigo.*
- *Weakness: bilateral or unilateral.*
- *Sensory symptoms (e.g. paraesthesiae):* may be confined to the face and, if unilateral, may be contralateral to weakness.
- *Ophthalmoplegia, gaze deviation, or dysconjugate eye movements:* in unilateral pontine lesions, conjugate gaze deviation is directed away from the lesion and towards the side of the hemiparesis if there is one. The reverse applies for frontal cortical strokes.
- *Horner's syndrome.*
- *Ptosis:* caused by a midbrain infarct in the absence of an accompanying third nerve palsy or Horner's syndrome is bilateral due to the levator subnucleus of the IIIrd nerve being in the midline.
- *Nystagmus.*
- *Hearing loss:* caused by damage to the VIIth nerve nucleus or fascicle.
- *Dysarthria or dysphagia.*
- *Ataxia:* which may be uni- or bilateral due to dysfunction of cerebellar connections.
- *Impaired level of consciousness:* ranges from transient loss of consciousness to coma.
- *Altered pattern of respiration.*

Signs associated with brainstem dysfunction are explained under ➡ Examination of brainstem function 1, pp. 460–1, ➡ Examination of brainstem function 2, p. 462, and ➡ Examination of brainstem function 3, pp. 464–5. They result because of damage either to the nuclei (including cranial nerve nuclei) within the brainstem, to the cranial nerves, or to the long tracts which traverse and/or decussate within the brainstem. 'Crossed signs' may occur in brainstem strokes, e.g. part of the lateral medullary/Wallenberg's syndrome consists of loss of pain and temperature sensation from the contralateral trunk and limbs (crossed spinothalamic) and ipsilateral loss of the same sensory modalities from the face (uncrossed trigeminal tract). There are a large number of other eponymous syndromes associated with damage to particular zones within the brainstem. Learning these is not particularly rewarding; better to concentrate on the principles of brainstem anatomy.²⁶

Causes

Thrombosis, embolism, haemorrhage, or vertebral artery dissection (especially following neck manipulation).

Assessment of severity

- Reduced level of consciousness and coma carry worse prognosis.
- Extent of brainstem dysfunction may be appreciated from systematic examination of brainstem function (➡ Examination of brainstem function 1, pp. 460–1; ➡ Examination of brainstem function 2, p. 462; ➡ Examination of brainstem function 3, pp. 464–5).
- Basilar occlusion carries a very poor prognosis (80% mortality).

Management

Consult a neurologist. The imaging modality of choice is MRI; this should be performed urgently to rule out other diagnoses. Some centres may consider intra-arterial thrombolysis in patients with basilar occlusion if the patient is referred swiftly. Urgent intervention is required for:

- Metabolic coma with brainstem depression, e.g. opiates (➡ Opioids, p. 770).
- Transtentorial herniation causing progressive brainstem compression (➡ Examination of brainstem function 3, pp. 464–5).
- Posterior fossa mass with tonsillar herniation causing brainstem compression.
- Cerebellar haemorrhage with/without brainstem compression (➡ Examination of brainstem function 3, pp. 464–5).

References

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Cerebellar stroke

Presentation

The triad of headache, nausea/vomiting, and ataxia is the classical syndrome. But it occurs in <50% of cases and, of course, is common in a number of other conditions. Patients present with symptoms and signs which are often attributed to brainstem or labyrinthine causes.^{27,28} Always consider the possibility of a cerebellar stroke as a serious alternative diagnosis because surgical decompression can be lifesaving if there is a mass effect within the posterior fossa. If the diagnosis is a possibility, ask for an urgent CT scan, or better still, an MRI.

- *Headache, nausea/vomiting*: sudden or progressive over hours to days. Location of headache varies widely.
- *Dizziness or true vertigo*: occurs in 30% of cases.
- *Visual disturbance*: diplopia, blurred vision, or oscillopsia.
- *Gait/limb ataxia*: most alert patients report or demonstrate this.
- *Nystagmus or gaze palsy*.
- *Speech disturbance*: dysarthria or dysphonia in 50% of alert patients.
- *Loss of consciousness*: may be transient, but many present in coma.
- *Hypertension*.

Predisposing factors

- Hypertension (>50%).
- Greater proportion of embolic cause of stroke in cerebellar infarction.
- Anticoagulants: there is a disproportionately higher risk of cerebellar haemorrhage (cf. intracerebral haemorrhage) in patients taking warfarin.
- Metastatic neoplasm.

Assessment of severity

Patients who present in coma, or subsequently develop it, will die unless they receive surgical treatment. There is debate about the prognosis of those who remain alert.

Management

Make a definitive diagnosis with an urgent CT scan. (Is there a haemorrhage/infarct? Is there distortion of the fourth ventricle and aqueduct with dilatation of the lateral ventricles?) Liaise with the regional neurosurgery unit early.

Priorities

- 1 Stabilize the patient and protect the airway (➡ Coma: assessment, pp. 348–9).
- 2 Correct the bleeding tendency or effects of anticoagulants.
- 3 Intensive care/high dependency ward nursing observations if the patient is not transferred to a neurosurgical centre immediately.
- 4 Definitive surgical decompression, if necessary and possible.

References

27. Dunne JW, Chakera T, Kermode S. Cerebellar haemorrhage—diagnosis and treatment: a study of 75 consecutive cases. *Q J Med* 1987;**64**:739–54.
28. [No authors listed]. Cerebellar stroke. *Lancet* 1988;**1**:1031–2.



Transient ischaemic attacks

Presentation

Sudden-onset focal deficit of cerebral function or monocular blindness resolving within 24h, but usually between a few minutes to 2h. The symptoms should have developed within a few seconds, and if several parts of the body (e.g. face, arm, leg) are involved, they should have been affected simultaneously without any 'march' or progression.

- *Symptoms of carotid TIA*: hemiparesis, dysphasia, or transient monocular blindness (amaurosis fugax) (➡ Cerebral infarction syndromes, p. 424).
- *Symptoms of posterior circulation/vertebrobasilar TIA*: bilateral or alternating hemiplegia or sensory symptoms, crossed motor/sensory signs (ipsilateral face, contralateral arm, trunk or leg deficit), quadriplegia. Sudden bilateral blindness. Two or more of: vertigo, diplopia, dysphagia, ataxia, and drop attacks if they occur simultaneously.
- *Symptoms of uncertain arterial territory origin*: hemianopia alone or dysarthria alone.
- *Symptoms very unlikely TIA*: syncope, loss of consciousness or confusion, convulsion, incontinence of urine or faeces, dizziness, focal symptoms associated with migrainous headache, scintillating scotoma.

Causes

Thrombosis or embolism (see Box 6.22 for risk factors).

Differential diagnosis

Many conditions may appear at first to be a TIA, e.g.:

- Cerebral tumour (primary or secondary).
- Brain abscess.
- Demyelination.
- Focal migraine.
- Subdural haematoma.
- Todd's paresis (post-seizure).
- Hypoglycaemic attack.
- Encephalitis.

Investigations

In patients with a suspected TIA in whom the vascular territory or pathology is uncertain, a diffusion-weighted MRI should be performed. If MRI is contraindicated (i.e. pacemaker, shrapnel, some brain aneurysm clips and heart valves, metal fragments in the eyes, and severe claustrophobia), CT scanning should be used.

Management

The objective is to prevent recurrence or a complete stroke. The risk of stroke must be assessed, using a validated scoring system such as the ABCD²*. For management of TIAs, see Box 6.26.

The ABCD²* is a prognostic score to identify people at high risk of stroke after a TIA. It is calculated based on:

- A: age (≥ 60 years, 1 point).
- B: BP at presentation ($\geq 140/90$ mmHg, 1 point).
- C: clinical features (unilateral weakness, 2 points; or speech disturbance without weakness, 1 point).
- D: duration of symptoms (≥ 60 min, 2 points; or 10–59 min, 1 point).

The calculation of ABCD² also includes the presence of DM (1 point). Total scores range from 0 (low risk) to 7 (high risk).

Box 6.26 Management key points: TIAs

- Exclude hypoglycaemia.
- If the history is compatible with TIA: start aspirin 300 mg.
- Specialist assessment and investigations within 24 h if ABCD² ≥ 4 or in cases of crescendo TIA (≥ 2 TIAs in a week) or patient on warfarin. Specialist assessment and investigations may be performed within 1 week if ABCD² < 4 .
- Best medical treatment: control of BP, antiplatelet drugs (high-dose aspirin 300 mg/day, followed by low-dose 75 mg aspirin or clopidogrel), cholesterol-lowering through diet and drugs (statins), smoking cessation.
- If the vascular territory or pathology is uncertain: diffusion-weighted MRI (or CT if MRI contraindicated) within 1 week of symptom onset.
- Carotid imaging if the patient is a candidate for carotid intervention within 1 week of symptom onset.
- If the level of symptomatic carotid stenosis is 70–99%: carotid endarterectomy within 2 weeks.

Further reading

Johnstone JC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 2007;**369**:283–92.

Confusional states and delirium: assessment

Up to 10% of acute medical admissions are complicated by acute confusion or delirium. The hallmark of *acute confusional states* is disorientation in time and place, impaired short-term memory, and impaired consciousness level. Typically, the patient is drowsy, with poor attention span and slowed mentation. In *delirium*, there are, in addition, disorders of perception such as hallucinations or illusions (misinterpreting shadows seen or sounds heard), and these may produce restlessness, agitation, and hyperactivity.

The main priority is to identify the cause of any treatable or life-threatening condition. Only a small minority (<10%) of patients will have a primary neurological disorder, and commonly there are multiple factors that may apply; these patients carry a good prognosis.

Assessment

- Assess the mental state: check for disorientation and memory impairment with the mini-mental test (see Box 6.27). An anxiety state can usually be distinguished by talking to the patient. Vivid hallucinations in the absence of a history of mental illness suggests alcohol withdrawal.
- Review the patient's notes, and try to obtain a history from friends/relatives of previous mental state or episodes of confusion. Patients with dementia are prone to confusion with intercurrent illness.
- Review the drug chart: benzodiazepines and narcotics may cause acute confusion in the elderly. Other drugs that may be involved are steroids, NSAIDs, β -blockers, and psychotropic medications.
- Assess the patient for acute illness: exclude faecal impaction and urinary retention. Relevant investigations are listed in Table 6.6.
- Examine for any focal neurological signs (pupils, limb power, reflexes, and plantar responses).
- In patients with prior high alcohol intake, examine for signs of liver disease, liver 'flap', and possible WE (nystagmus, ataxia, ophthalmoplegia).

Box 6.27 Mini-mental examination for the elderly

- 1 Age.
- 2 Time (nearest hour).
- 3 42 West Street: address for recall at the end of the test (make the patient repeat the address to check).
- 4 Year.
- 5 Place (name of hospital).
- 6 Recognition of two people (doctor, nurse, etc.).
- 7 Date of birth (day and month).
- 8 Year of World War 1 (or 2).
- 9 'Who is on the throne at the moment?'
- 10 Count backwards from 20 to 1.

Each correct answer scores 1 point. Healthy elderly people score 8.

Hodkinson, HM; Evaluation of a mental test score for assessment of mental impairment in the elderly, *Age and Ageing* 2012; 41 (suppl_3): iii35–iii40, doi.org/10.1093/ageing/afs148. Reprinted by permission of Oxford University Press on behalf of the British Geriatrics Society.

Table 6.6 Differential diagnosis and investigations

Differential diagnosis	Investigations
<i>Systemic disorder</i> ● Sepsis ● Alcohol withdrawal ● Metabolic disorder: • ↓ or ↑ glucose, Na⁺, or Ca²⁺ • Vitamin deficiency • Endocrine disease (thyroid, adrenal cortex) ● Myocardial ischaemia ● Organ failure (renal, respiratory, liver, cardiac) ● Organ failure (renal, respiratory, liver, cardiac)	Check urine, blood cultures, WBC, CRP, CXR, U&Es, glucose, LFTs, Ca²⁺, ABGs, pH, ECG, cardiac enzymes Consider Mg²⁺, amylase, porphyrins, thiamine, vitamin B₁₂, folate, thyroid-stimulating hormone (TSH), free T4
<i>Drug toxicity</i>	Check prescribed medication, serum alcohol/drug screen
<i>CNS disorder</i> ● Dementia ● Cerebrovascular accident (CVA) (especially non-dominant parietal lobe) ● Intracranial bleed (SAH, subdural) ● Infection (encephalitis, meningitis) ● Trauma ● Malignancy (primary or secondary) ● Post-ictal; non-convulsive status ● Cerebral vasculitis (SLE, PAN)	Consider CT scan with contrast, LP, EEG, blood cultures, CRP, syphilis serology, Lyme serology
<i>Malignancy</i>	Check CXR ± CT chest, serum Ca²⁺, CT brain

Confusional states and delirium: management

Management

(See Box 6.28.)

- Treat the cause. Nurse in a moderately lit room, with repeated reassurance. See if a family member can stay with the patient.
- Avoid sedation unless: (1) to facilitate essential tests and treatment for the patient's benefit; (2) the patient is a danger to themselves or others; and (3) relieving distress in a highly agitated or hallucinating patient.
- Use lorazepam 0.5–1mg PO/IM or otherwise haloperidol 0.5–1mg bd PO (or 2.5mg IM). Observe the effect on the patient for 15–20min, and repeat if necessary. In patients with cardiac or respiratory failure, correcting hypoxia may calm the patient by itself. Clomethiazole is indicated for confusion due to alcohol withdrawal (➡ Acute alcohol withdrawal, pp. 436–7).

Box 6.28 Management key points: acute confusional states

- Nurse in a moderately lit room, with repeated reassurance. See if a family member can stay with the patient.
- Sedation if agitated and aggressive, e.g. lorazepam (0.5–1mg PO or IM) or haloperidol (0.5–1mg bd PO or 2.5mg IM), but can worsen Lewy body dementia. Observe the effect for 15–20min, and repeat if necessary.

Identify and treat the underlying cause

- *Hypoxia*: maintain the airway; give O₂.
- *Hypoglycaemia*: 50mL of 50% glucose (remember to give IV thiamine before glucose if malnourishment/alcoholism is likely).
- *Vascular* (intracerebral bleed, infarction, or subdural haematoma): see ➡ Intracranial space-occupying lesion, p. 394–5; ➡ Extradural haemorrhage, p. 396; ➡ Intracerebral haemorrhage, p. 398–9, ➡ Subdural haematoma, p. 400–1; ➡ Subarachnoid haemorrhage: assessment, p. 402.
- *Infection* (intracranial: meningitis/encephalitis; extracranial, e.g. pneumonia or UTI, particularly in the elderly): antibiotics/antiviral treatments.
- *Trauma*: see ➡ Head injury: presentation, p. 380.
- *Tumours* (and other SOLs): dexamethasone; liaise with neurosurgeons.
- *Toxic* (e.g. alcohol intoxication/withdrawal or ODs) or *metabolic causes* (e.g. electrolyte disturbances, renal failure, liver failure, vitamin deficiencies, or endocrinopathies): correct the underlying cause; liaise with the appropriate specialist teams.
- *Inflammatory* (cerebral vasculitides): liaise with neurologists and rheumatologists.
- *Post-ictal*.



Acute alcohol withdrawal

Minor symptoms may be managed at home by the GP or a community drug and alcohol team, but in severe or complex cases, hospital admission is indicated. Acute alcohol withdrawal may also occur in hospital inpatients (where the alcohol history may have been missed initially), typically after 12–48h following admission, or as a comorbidity to an A&E presentation, e.g. GI bleed, falls. Indications for admission can be found in Chapter 13 on alcohol withdrawal (➡ Acute alcohol withdrawal, pp. 718–19).

Presentation

- Initial symptoms include anxiety and tremor, hyperactivity, sweating, nausea and retching, tachycardia, hypertension, and mild pyrexia. These symptoms peak at 12–30h and subside by 48h.
- Generalized tonic–clonic seizures may also occur during this period, but status epilepticus is unusual. Typically, these may not show the EEG characteristics of epilepsy and may be precipitated by flickering lights or other photic stimulation.
- Delirium tremens ('DTs') occurs in <5% of individuals, usually after 3–4 days of cessation of alcohol intake. It is associated with an untreated mortality of 15%. Features include:
 - Coarse tremor, agitation, confusion, delusion, and hallucinations.
 - Fever (occasionally severe), sweating, tachycardia.
 - Rarely lactic acidosis or ketoacidosis.
 - Also look for hypoglycaemia, Wernicke–Korsakoff syndrome, subdural haematoma, and hepatic encephalopathy.

Management

General measures

- Nurse in a well-lit room to prevent disorientation. Rehydrate (IV fluids, if necessary; avoid saline in patients with known chronic liver disease). Monitor urine output.
- Vitamin supplements: in uncomplicated alcohol withdrawal, to prevent WE, use thiamine IM/IV therapy (e.g. Pabrinex® one pair of ampoules daily. IV *slowly*—watch for signs of anaphylaxis) for 3–5 days). In suspected WE cases, see treatment under ➡ Wernicke–Korsakoff syndrome, p. 437.
- Monitor blood glucose for hypoglycaemia, and treat if necessary.
- Severe hypophosphataemia may complicate alcohol withdrawal and should be treated with IV PO_4^{3-} (polyfusor phosphates) if serum PO_4^{3-} is <0.6mmol/L (➡ Hypophosphataemia, p. 576).
- Exclude intercurrent infection (pneumonia, skin, urine).

Medically assisted alcohol withdrawal

- Long-acting benzodiazepines, such as chlordiazepoxide or diazepam are commonly used; lorazepam is not metabolized by the liver and may be used in liver disease.
- Carbamazepine is as effective as benzodiazepines, but side effects limit its use.
- For DT, use lorazepam PO as first line, if parenteral medication is required, use lorazepam, but olanzapine and haloperidol (↑ risk of seizure and cardiotoxicity) may be considered too, though 'off label'.

Wernicke–Korsakoff syndrome

- WE comprises the triad of ophthalmoplegia (nystagmus, VIth nerve palsy), ataxia (cerebellar type), and confusional state. In Korsakoff's syndrome, confusion predominates, often with overt psychosis, amnesia (antegrade and retrograde), and confabulation. Withdrawal symptoms may also occur.
- Diagnosis: reduced red cell transketolase activity (not usually available).
- Treat with IV thiamine (Pabrinex®), two pairs of ampoules tds for 2 days; if no response, discontinue; if there is an improvement, continue one pair of ampoules IM/IV daily for 5 days or as long as improvement continues. Ongoing oral thiamine treatment should follow parenteral thiamine.

Seizures

- Withdrawal seizures are typically self-limiting; if needed, use IV diazepam (Diazemuls®) 10mg over 5min (➡ Status epilepticus (tonic–clonic) 1, pp. 408–9).
- The most important issue here is to prevent the occurrence of seizures in the first place. This is mainly achieved by treating the patient with an appropriate alcohol withdrawal regime, usually chlordiazepoxide or diazepam (see Box 6.29 and Table 6.7). Consider adding lorazepam to prevent further seizures.
- Review the reducing withdrawal regime if the seizure occurred while already on a regime, as it may be suboptimal or reducing too quickly.
- A carbamazepine regime may be used for treatment of alcohol withdrawal; however, evidence shows this is not superior to benzodiazepines in seizure prevention, and combining both conferred no added benefit.
- Phenytoin is no longer recommended to treat alcohol withdrawal seizures.

Follow-up

Arrange a referral to an alcohol dependence clinic.

Box 6.29 Management key points: acute alcohol withdrawal

- Nurse in a well-lit room to prevent disorientation.
- Rehydrate (IV fluids, if necessary; avoid saline in patients with known chronic liver disease).
- Correct electrolyte disturbances (hypokalaemia, hypomagnesaemia, and severe hypophosphataemia).
- Prophylaxis of WE: IM/IV Pabrinex® one pair of ampoules daily for 3–5 days.
- Reducing-regimen chlordiazepoxide or diazepam (reduce the dose in liver disease or use lorazepam). Alternatively, reducing regimen of carbamazepine: start at 800mg daily in divided doses, reducing gradually over 5 days to 200mg daily; usual treatment duration 7–10 days.
- Treat intercurrent infection (e.g. pneumonia, skin, urine).
- Monitor vital signs, urine output, and blood glucose for hypoglycaemia.

Table 6.7 Titrated fixed-dose chlordiazepoxide protocol for treatment of alcohol withdrawal

Typical recent daily consumption	15–25 units	30–49 units	50–60 units
Severity of alcohol dependence	MODERATE SADQ score 15–25	SEVERE SADQ score 30–40	VERY SEVERE SADQ score 40–60
Starting doses of chlordiazepoxide	15–25mg qds	30–40mg qds	50mg qds
Day 1 (starting dose)	15 qds	30 qds	50 qds*
Day 2	10 qds	25 qds	45 qds
Day 3	10 tds	20 qds	40 qds
Day 4	5 tds	15 qds	35 qds
Day 5	5 bd	10 qds	30 qds
Day 6	5 nocte	10 tds	25 qds
Day 7		5 tds	20 qds
Day 8		5 bd	10 qds
Day 9		5 nocte	10 qds
Day 10		5 bd	10 tds
Day 11		5 nocte	5 tds
Day 12			bd
Day 13			5 nocte

* Doses of chlordiazepoxide in excess of 30mg qds should only be prescribed in cases where severe withdrawal symptoms are expected, and the patient's response to treatment should always be regularly and closely monitored. Doses in excess of 40mg qds should only be prescribed where there is clear evidence of very severe alcohol dependence. Such doses are rarely necessary in women and never in the elderly or where there is severe liver impairment.

Alcohol-Use Disorders: The NICE guideline on Diagnosis, Assessment and Management of Harmful Drinking and Dependence. National Clinical Practice Guideline 115. National Collaborating Centre for Mental Health.

Neuromuscular respiratory failure: assessment

Presentation

A number of disorders of the peripheral nerve, neuromuscular junction, or muscle may present with hypercapnic (type 2) respiratory failure or impending failure. There are many differences between these conditions, but consider the diagnosis in the presence of the following features:

- *Limb weakness*: progressing over hours or days with diminished/no reflexes but no UMN signs.
- *Neck flexion/extension weakness*: typical for many causes. Often mirrors bulbar dysfunction.
- *Muscular tenderness or pain*: may be a feature (e.g. back pain in GBS, limb pain in radiculitis/plexopathy or vasculitic neuropathy, muscle pain in inflammatory myopathy).
- *Facial weakness*.
- *Ptosis* (myasthenia, botulism, Lambert–Eaton, myopathy).
- *Bulbar dysfunction*: is a particularly ominous sign because it may lead to improper clearance of secretions and aspiration.
- *Paradoxical abdominal movement*: if the diaphragm is paralysed, it moves passively into the thorax, with a fall in intrapleural pressure produced by expansion of the ribcage in inspiration. As a result, the anterior abdominal wall also moves in (rather than out) during inspiration.
- *Dyspnoea or distress in supine position*: if the diaphragm is paralysed, movement of abdominal contents towards the thorax is more prominent when the patient lies flat because gravity no longer acts to counteract this passive movement. As a result, the volume of air inspired is reduced. This is a rare, but important, cause of orthopnoea.
- *Sensory symptoms*: may be present with or without glove-and-stockings sensory loss.
- *Autonomic instability*: may be a prominent feature of GBS and may lead to cardiac arrest.
- *Pneumonia*: in known neuromuscular disease.
- *Respiratory arrest*: a common pitfall is to consider the degree of respiratory distress unimpressive. Peripheral weakness, in combination with an expressionless ‘myopathic’ facies, may lead to a false sense of well-being when the patient may, in fact, be confronting an impending respiratory arrest.

Assessment of severity

- Measurement of forced vital capacity (FVC) is *mandatory* (measured with Wright respirometer available from an anaesthetic nurse or ICU). Note that O_2 saturations, peak flow rate, and forced expiratory volume in 1s (FEV_1) *do not correlate* with the degree of neuromuscular impairment.
 - FVC $<30\text{mL/kg}$ causes impaired clearance of secretions.
 - FVC $<15\text{mL/kg}$ suggests ventilatory failure and is an indication for immediate intubation and ventilation, regardless of other parameters of respiratory function.
- ABGs: hypercapnia occurs relatively late.
- CXR: to determine the extent of consolidation if there is concomitant aspiration or infective pneumonia. Subtle linear atelectasis is often seen as a direct result of reduced lung volume.

Neuromuscular respiratory failure: investigations and management

For investigations of neuromuscular respiratory failure, see Box 6.30.

Management

- Assess severity and measure FVC frequently.
- Consider intubation and ventilatory support if in adults FVC <1L or 15mL/kg (or there is a progressive decline). Do not use suxamethonium as a muscle relaxant. It may cause a sudden rise in K⁺ in patients with denervated muscles.
- Liaise with the neurologist early. Consider transfer to a regional neurology unit if the patient is well and FVC >25mL/kg and stable. If the patient is unwell and FVC <15mL/kg or falling precipitously from a higher level, intubate electively and then consider transfer. All patients should be accompanied by an anaesthetist.
- For investigations, see Table 6.8. Most of these conditions will not come into the differential, but it is advised that blood be taken for virology screen and autoimmune profile, and 20mL be saved for retrospective analysis if required.
- ECG monitoring and frequent observation of BP and pulse are required if GBS is suspected, because there is a high incidence of autonomic instability.
- Consider specific therapies (see Table 6.8) and:
 - GBS (➡ Guillain–Barré syndrome, pp. 452–3).
 - Myasthenia gravis (➡ Myasthenic crises, pp. 444–6).
 - Botulism (➡ Botulism, pp. 454–5).
 - Heavy metal intoxication (➡ Drug overdoses and antidotes, pp. 742).
 - Organophosphate exposure (➡ Drug overdoses and antidotes, p. 742).
 - Porphyria.
 - Rhabdomyolysis (➡ Rhabdomyolysis, pp. 306–7).
- SC heparin prophylaxis for DVT.
- Enteral nutrition should be considered early.

Box 6.30 Investigations for neuromuscular respiratory failure

- FBC, U&Es, CK, ESR, CRP.
- FVC.
- ABGs.
- CXR.
- NCS/EMG.
- Anti-acetylcholine receptor (AChR) antibody/Edrophonium test/ice test.
- CT/MRI scan for brainstem/cervical cord pathology.
- Nerve biopsy, muscle biopsy.
- Urine/plasma toxin screen (see Table 6.8).

Table 6.8 Neuromuscular respiratory failure

Condition	Investigation	Specific treatments
<i>Central nervous system disease</i>		
Brainstem disease	● MRI scan	● Reduce ICP ● Decompress
Spinal cord disease	● MRI scan	● Decompress
<i>Peripheral neuropathies</i>		
GBS (➡ Guillain–Barré syndrome, pp. 452–3)	● NCS	● IV immunoglobulin (IVIG) ● Plasma exchange
Organophosphates	● Red cell cholinesterase ● Plasma pseudo-cholinesterase	● Atropine ● Pralidoxime
Heavy metals: lead, thallium, gold, arsenic	● Blood and urine levels	● Specific antidote (➡ Drug overdoses and antidotes, p. 742)
Drugs (e.g. vincristine)		● Stop drug
Malignancy	● Nerve biopsy	● Cytotoxics
Vasculitis (e.g. SLE)	● Nerve biopsy	● Immunosuppressants
Metabolic (porphyria)	● Urinary porphyrins	● Avoid precipitants ● IV glu/haematin
Diphtheria	● Throat swab	● Antitoxin
<i>Neuromuscular junction disease</i>		
Myasthenia gravis	● Anti-AChR Ab ● Edrophonium test	● Steroids ● IVIG, plasma exchange
Anti-cholinesterase OD	● –ve Edrophonium test	● Stop drug
Hypermagnesaemia	● Plasma Mg^{2+}	● IV Ca^{2+}
Botulism (➡ Botulism, pp. 454–5)		● Antitoxin
<i>Muscle disease</i>		
Hypokalaemia	● Plasma K^+	● K^+ replacement
Hypophosphataemia	● Plasma PO_4^{3-}	● PO_4^{3-} replacement
Polymyositis	● EMG ● Muscle biopsy	● Steroids
Acute rhabdomyolysis (➡ Rhabdomyolysis, pp. 306–7)	● EMG ● Muscle biopsy	● IV hydration ● Urine alkalinization

Myasthenic crises

Presentation

- *Generalized weakness*: usually worse proximally, and classically painless and fatiguable. There may be ptosis and diplopia. Reflexes and sensation are normal. Patients with pure ocular myasthenia for >2 years rarely generalize.
- *Dyspnoea*: the patient may not, at first glance, appear very distressed. An expressionless myopathic facies, together with weak muscles of respiration, may give a false sense of well-being.
- *Bulbar dysfunction*: is potentially dangerous, as it may lead to impaired clearance of secretions and aspiration pneumonia.
- *Exhaustion and ventilatory failure*: leading to coma.
- *History of penicillamine use*: may cause a syndrome identical to idiopathic myasthenia gravis.²⁹

Common predisposing factors

Infection, surgery, and drugs (see Box 6.31). NB Corticosteroids used to treat myasthenia can initially lead to an acute crisis (so start low and go slow).

Assessment of severity

- Vital capacity is the most useful indicator. ABGs are not sensitive enough and demonstrate hypercarbia late.
- Bulbar dysfunction.

Cholinergic crisis

It may not be possible on clinical evaluation to distinguish between worsening myasthenia and excessive anticholinesterase treatment (which leads to weakness by producing depolarization block). Consider withdrawing anticholinesterases only after consulting a neurologist. Note that cholinergic crisis is very rare, compared to myasthenic crisis.

Management

- Stabilize the patient: protect the airway; intubate and ventilate if necessary. Ensure there are no electrolyte disturbances ($\downarrow K^+$, $\downarrow Ca^{2+}$, $\uparrow Mg^{2+}$) or drugs prescribed which exacerbate weakness.
- Consider Tensilon® (edrophonium) test (➡ Tensilon® (edrophonium) test, p. 445). Anticholinesterase treatment may be helpful if cholinergic crisis is excluded. If there is no effect with Tensilon®, reconsider the diagnosis. Withhold all anticholinesterase medications for 72h. The Tensilon® test may be repeated at intervals.
- Immunosuppression should be supervised by a neurologist: prednisolone 60–80mg/day produces improvement after 10–12 days but should be introduced with care (start low and go slow) because there may be initial worsening of weakness. High-dose steroids are given until remission occurs. Azathioprine (2.5mg/kg) has also been used for maintenance therapy but takes months to have an effect.
- Plasmapheresis is used to remove circulating antibody. It usually involves exchange of 50mL/kg/day over several days. Most centres use IVIG therapy, instead of plasmapheresis.

- Regular anticholinesterase inhibitor therapy should be directed by a neurologist. Therapy depends upon response, but one initial strategy is to commence with pyridostigmine 60mg q4h. This can be given by NG tube or, if necessary, IM neostigmine can be used instead (1mg neostigmine should be given for every 60mg pyridostigmine).

Tensilon® (edrophonium) test

- 1 A history of asthma or cardiac dysrhythmias are relative contraindications. Atropine should be drawn up prior to the test, in case edrophonium (an inhibitor of acetylcholinesterase) produces a severe cholinergic reaction, e.g. symptomatic bradycardia.
- 2 Prepare and label two 1-mL syringes: one containing saline, the other 10mg of edrophonium.
- 3 Select a muscle to observe for the test, and ask a colleague to assess its strength prior to the test.
- 4 Inject, in stages, the contents of either syringe, keeping both patient and colleague blinded to the contents of each syringe. Ask the observer to reassess muscle strength after the contents of each syringe have been injected.
- 5 Edrophonium should first be given as a bolus of 2mg (0.2mL), and untoward cholinergic effects should be observed for. If it is tolerated, the remaining 0.8mL can be given 1min later.
- 6 Improvement in muscle strength following edrophonium suggests the patient is suffering a myasthenic, not cholinergic, crisis.

Box 6.31 Drugs which may exacerbate myasthenia

Antibiotics

- Gentamicin.
- Neomycin.
- Colistin.
- Tetracycline.
- Tobramycin.
- Clindamycin.
- Streptomycin.
- Kanamycin.
- Lincomycin.

Cardiac drugs

- Quinidine.
- Propranolol.
- Quinine.
- Procainamide.

Local anaesthetics

- Lidocaine.
- Procaine.

Anticonvulsants/psychotropic drugs

- Phenytoin.
- Lithium.
- Barbiturates.
- Chlorpromazine.

Muscle relaxants

- Suxamethonium.
- Curare.

Analgesics

- Pethidine.
- Morphine.

Hormones

- Corticosteroids (initially).
- Thyroxine.

Others

- Mg²⁺ salts.

Ice test

- 1 The test consists of the application of ice to the eyes for 2–3min, ensuring that the ice is covered (e.g. in a bag) to prevent ice burns. Avoid prolonged exposure (cold burns and false negatives).
- 2 If positive, the patient's ptosis improves.
- 3 The results of the test can be deemed positive with an improvement of the patient's diplopia or a raise of 2mm of the palpebral fissure following the removal of the ice pack.³⁰

References

29. Thomas CE, Mayer AS, Gungor Y, et al. Myasthenia gravis: clinical feature, mortality, complications, and risk factors for prolonged intubation. *Neurology* 1997;**48**:1253–60.
30. Sethi KD, Rivner MH, Swift TR. Ice pack test for myasthenia gravis. *Neurology* 1987;**37**:1383–5.

Spinal cord compression: assessment

Presentation

- **Back pain:** is usually the first symptom. It often starts weeks before other features and becomes progressively unremitting, keeping the patient awake at night. There may also be *thoracic dermatomal pain* which is misinterpreted and leads to a long and unrewarding search for the cause of chest or abdominal pain.
- **Sensory symptoms:** such as paraesthesiae or a sensation of limb heaviness or pulling, may then occur.
- **Sensory loss:** may be apparent as a sensory level on testing. It is wise to test for pin-prick (spinothalamic function) and joint position sense/vibration sense (dorsal column function)—anterior or posterior portions of the cord may be selectively compressed. ‘Sacral sparing’ refers to preservation of sensation in (usually) S3–S5 dermatomes; it is a relatively reliable sign of an intramedullary lesion (see Box 6.32) which initially spares laterally placed spinothalamic tract fibres subserving sacral sensation. Note that a sensory level only indicates the lowest possible level of the lesion—it may well be several segments higher.
- **Weakness:** is often first described as clumsiness but soon progresses to clear loss of power.
- **Autonomic dysfunction:** if the sympathetic pathways are involved, especially in high thoracic or cervical lesions, hypotension, bradycardia, or sometimes cardiac arrest may occur. This may be triggered by noxious stimuli such as pain, UTI, or abdominal distension caused by constipation or bladder outflow obstruction.
- **Sphincter dysfunction:** commences as hesitancy or urgency of micturition and may progress to painless urinary retention with overflow. Constipation is another consequence of cord compression.
- **Fever:** should alert one to the possibility of an infectious cause.
- **Respiratory failure:** occurs with high cervical cord compression and is one cause of acute neuromuscular respiratory paralysis (➡ Neuromuscular respiratory failure: assessment, pp. 440–1).
- **Conus medullaris lesions:** compress the sacral segments of the cord and lead to relatively early disturbance of micturition and constipation, impotence, reduced perianal sensation and anal reflex; rectal and genital pain occurs later. Plantar responses are extensor.
- **Cauda equina lesion:** lesions at or below the first lumbar vertebral body may compress the spinal nerves of the cauda equina, leading to a flaccid, flexic, and often asymmetric paraparesis. Lumbosacral pain occurs early; bladder and bowel dysfunction appears relatively late. A sensory level is found in a saddle distribution up to L1 (corresponding to roots carried in the cauda equina).
- **Combined conus and cauda lesions:** produce a combination of LMN and UMN signs.
- **General examination:** remember that a common cause is malignant compression from metastatic disease. Perform a careful examination, including the breasts, testicles, and thyroid if appropriate.

Assessment of severity

The degree of weakness, sensory loss, and sphincter dysfunction are useful indicators of severity.

Box 6.32 Causes of non-traumatic spinal cord compression

- Tumours:
 - *Primary*: intradural + extramedullary: schwannoma, meningioma; intradural + intramedullary: astrocytoma, ependymoma.
 - *Metastatic (usually extradural)*: breast, prostate, lung, thyroid, GIT, lymphoma, myeloma.
- Infection: staphylococcal abscess, tuberculoma, infected dermoid.
- Prolapsed intervertebral disc (central).
- Cyst: arachnoid, syringomyelia.
- Haemorrhage.
- Skeletal deformity: kyphoscoliosis, achondroplasia, spondylolisthesis.

Spinal cord compression: management

This depends on the diagnosis and condition of the patient. If the diagnosis is unknown, it is imperative to make it swiftly and discuss the case with the regional neurosurgical centre. If the patient is known to have neoplastic disease and malignant compression is very likely, urgent radiotherapy is the first-line therapy in most, but not all, cases. In some patients with disseminated disease, it may not be appropriate to make any intervention, apart from analgesia. Always consult a senior oncologist.

- Plain X-rays of the spine are sometimes used as initial investigation but should not delay definitive imaging. These may show vertebral collapse, lytic lesions, or sclerosis. Perform a CXR to look for malignancy.
- MRI is the investigation of choice. This should be arranged urgently. If facilities are not available locally, discuss with the regional neurosurgical centre.
- The use of steroids is an important component of the initial management of epidural spinal cord compression. However, the optimal dose and schedule remain uncertain. Some experts recommend a bolus of dexamethasone 10mg IV, followed by 16mg/day PO in divided doses for patients with minimal neurologic symptoms. The dose is gradually reduced once definitive treatment is well under way. In patients with paraparesis/paraplegia, high-dose dexamethasone may be given (96mg IV, followed by 24mg qds for 3 days), and the dose can be tapered over 10 days (halve the dose every 3 days).
- A PPI should be given for gastric protection.
- If the cause of compression appears to be infective (fever, neutrophilia, raised CRP, etc.), blood, sputum, and urine cultures should be sent.
- Monitor haemodynamics and watch for autonomic dysfunction. Control pain and act to prevent constipation.
- If there is bladder dysfunction, urinary catheterization may be necessary. If immobile, start prophylactic SC heparin (5000U tds).
- If there is high cervical compression or if ventilation appears to be compromised, FVC and ABGs should be measured. Indications for intubation (if this is appropriate) are discussed under ➡ Neuromuscular respiratory failure: assessment, pp. 440–1.
- If a diagnosis is not apparent and immediate neurosurgical action is not indicated, discuss with radiology with a view to CT-guided biopsy.

See Box 6.33 for key points in management of spinal cord compression.

Box 6.33 Management key points: spinal cord compression

- Establish the diagnosis:
 - Urgent MRI, CXR (? malignancy).
 - If the cause appears to be infective (fever, neutrophilia, raised CRP): send blood, sputum, and urine cultures.
- Discuss the case with the regional neurosurgical centre, and consult a senior oncologist regarding advice for urgent radiotherapy for neoplastic disease and malignant compression.
- Corticosteroids:
 - Patients with minimal neurologic symptoms: a bolus of dexamethasone 10mg IV, followed by 16mg/day PO in divided doses.
 - Patients with paraparesis/paraplegia: dexamethasone 96mg IV, followed by 24mg qds for 3 days, and the dose can be tapered over 10 days. A PPI should be given for gastric protection.
- Control pain and act to prevent constipation.
- Urinary catheterization if there is bladder dysfunction.
- Prophylactic SC heparin if immobile.
- Monitor ABG and FVC in cases of high cervical compression or compromise.
- Monitor haemodynamics and watch for autonomic dysfunction.

Guillain–Barré syndrome

Presentation

- *Progressive weakness of more than one limb*: in an individual who may recently have experienced a mild respiratory or GI febrile illness. Weakness is as commonly proximal as distal. It is usually symmetrical but may be asymmetrical.
- *Diminished tendon reflexes/areflexia*: is typical.
- *Sensory symptoms*: paraesthesiae often precedes weakness. Sensory loss is not usually profound, although there may be a glove-and-stocking distribution impairment of two-point discrimination, joint position, and vibration sense. If there is a sensory level, spinal cord compression (➡ Spinal cord compression: management, p. 450) should be the diagnosis, until proven otherwise.
- *Limb or back pain*: is a major symptom in 30%. Back pain can precede symptoms of weakness.
- *Cranial nerve dysfunction*: occurs in 50%. Bulbar function and muscles of mastication are affected in 30%; ocular muscles in 10% of patients.
- *Ventilatory failure*: see ➡ Neuromuscular respiratory failure: assessment, pp. 440–1.
- *Autonomic dysfunction*: is common—sweating, tachycardia, sudden swings of BP, dysrhythmias, and cardiac arrest. Bladder or bowel dysfunction occurs, but if it is present from the outset or if it is persistent, reconsider the diagnosis.
- *Miller–Fisher variant*: ophthalmoplegia (giving rise to diplopia), ataxia, and areflexia, without significant weakness or sensory signs. Associated with anti-GQ1b antibodies in the serum.

Causes

GBS probably represents an immune-mediated attack on peripheral nerves. Infections which may precede it include CMV, *Campylobacter jejuni*, EBV, hepatitis B, *Mycoplasma*, and HSV.

Assessment of severity

Poor prognostic features on presentation include:

- Rapid onset.
- Requirement for ventilation (bulbar compromise, reducing vital capacity, respiratory failure).
- Age >40 years.
- Reduced amplitude of compound muscle action potential (<10% of control) and extensive spontaneous fibrillation in distal muscles suggesting denervation (NB electrophysiological studies may be normal in early GBS).
- Presence of autonomic dysfunction.
- Axonal variant (often with preceding *C. jejuni* infection).

A grading system has been devised to follow a patient's progress:

- Grade 1: able to run.
- Grade 2: able to walk 5m but not to run.
- Grade 3: able to walk 5m with assistance.
- Grade 4: chair-/bed-bound.
- Grade 5: ventilated.

Practice points

Acute onset of bilateral facial palsy is usually due to GBS. Long-standing bilateral facial weakness is usually due to sarcoid, HIV, facial-onset sensorimotor neuropathy, or Lyme disease.³¹

Management

It is important to appreciate that GBS is a diagnosis of exclusion, with an extensive differential. The pace at which alternative diagnoses need to be excluded depends upon the history and findings.

Management of a patient with GBS is that of any patient with neuromuscular paralysis, although there are a few important specific measures:

- *Monitor FVC* twice daily.
- *Autonomic instability* is a common feature, so ECG monitoring and frequent assessment of BP and pulse are advisable, particularly in any patient with bulbar or respiratory involvement (NB tracheal suction may lead to bradycardia or asystole).
- *CSF analysis* may be required. CSF protein may be normal initially but characteristically rises markedly and peaks in 4–6 weeks. If CSF lymphocytes are prominent in number, consider HIV seroconversion.
- *Steroids* are of no benefit in GBS and can worsen matters.
- *Plasma exchange* is proven to be better than supportive treatment alone. IVIG (0.4g/kg for 5 days) is as effective as plasma exchange and is currently the standard treatment. Therapy should not be commenced without prior discussion with a neurologist.
- *DVT prophylaxis*.

For key points in the management of GBS, see Box 6.34.

Prognosis

Around 65% are able to resume manual work; 8% die in the acute stage (usually from autonomic dysfunction or PE), and the remainder are left with residual disability. The prognosis is worse in those with more severe disease.

Box 6.34 Management key points: Guillain-Barré syndrome

- Management of GBS is that of any patient with neuromuscular paralysis.
- Monitor FVC twice daily at least.
- Autonomic instability is a common feature (monitor ECG, BP, and HR).
- Plasma exchange.
- IVIG (0.4g/kg for 5 days) appears to be as effective as plasma exchange.
- Therapy should not be commenced without prior discussion with a neurologist.
- DVT prophylaxis.

References

31. Winer JB. An update in Guillain-Barré syndrome. *Autoimmune Dis* 2014;2014:793024.

Botulism

Presentation

Botulism is caused by exotoxins of *Clostridium botulinum*. There are three syndromes: food-borne, SC drug users wound, and infantile. The latter two causes are rare and will not be discussed here. The most common form of botulism is food-borne, with outbreaks usually attributed to canned food. Patients present with symptoms usually within 18h of ingestion of the toxin (see Box 6.35):

- Sore throat, fatigue, dizziness, blurred vision.
- Nausea, vomiting, constipation.
- Rapidly progressive weakness, often beginning in the extraocular and/or pharyngeal muscles and descending symmetrically in severe cases to give upper and lower limb paralysis and respiratory failure (➡ Neuromuscular respiratory failure: assessment, pp. 440–1; ➡ Neuromuscular respiratory failure: investigations and management, p. 442).
- Paraesthesiae may occur, but there are no sensory signs.
- Parasympathetic dysfunction causes a dry mouth, ileus, and dilated non-reactive pupils in an alert patient. This pupillary response may help to distinguish botulism from other neuromuscular disorders; however, in most cases, the pupils remain reactive.

Wound botulism is similar, except GI upset does not occur.

Assessment of severity

Limb weakness and ventilatory failure are indicators of severe disease. Patients with these features have a worse prognosis, as do patients >20 years and those who have ingested type A toxin.

Management

- Assess severity; *measure FVC frequently*, and attempt to exclude other important causes of neuromuscular failure (➡ Neuromuscular respiratory failure: assessment, pp. 440–1). In particular, a *Tensilon*[®] test should be performed to exclude myasthenia gravis (➡ Tensilon[®] (edrophonium) test, p. 445); *nerve conduction* should be normal, but it is important to exclude GBS (➡ Guillain–Barré syndrome, pp. 452–3); *EMG* is frequently abnormal in botulism (decrement of compound muscle action potential at slow rates of repetitive stimulation of 3s⁻¹ and facilitation of motor response at rapid rates of 50s⁻¹). Serum and stool should be assayed for toxin and *C. botulinum*.
- *General management* is described elsewhere (➡ Neuromuscular respiratory failure: assessment, pp. 440–1; ➡ Neuromuscular respiratory failure: investigations and management, p. 442).
- *Specific treatment*: if botulism is suspected, 10 000U of trivalent (A, B, E) antitoxin should be administered IV immediately and at 4-hourly intervals. ~20% of patients have minor allergic reactions to this and require corticosteroid and antihistamines, as for anaphylaxis (for supplies outside normal working hours, contact Department of Health Duty Officer (UK), tel: 020 7210 3000).

- *Guanidine hydrochloride* (an acetylcholine agonist) may be of benefit in some patients (35–40mg/kg/day PO in divided doses).
- Gastric lavage, emetics, cathartics, and enemas may be used with caution to accelerate elimination of toxin from the GIT. The first two interventions are contraindicated if bulbar weakness is present; Mg^{2+} -containing cathartics should not be used, as there is a risk that Mg^{2+} may enhance toxin activity.

Box 6.35 Pathophysiology of botulism

Preformed botulinum toxin is a potent presynaptic blocker of acetylcholine release at the neuromuscular junction, post-ganglionic parasympathetic terminals, and autonomic ganglia. There are six antigenically distinct toxins (A–F), but only A, B, and E appear to be associated with human illness.

Tetanus

Presentation

Tetanus is caused by the effects of exotoxins produced by *Clostridium tetani*. It occurs after *C. tetani* spores have gained access to tissues. The wound may be very trivial, and in 20% of cases, there is no history or evidence of injury. Incubation of spores may take weeks, but most patients present within 15 days with:

- Pain and stiffness of the jaw.
- Rigidity and difficulty in opening the mouth: trismus or 'lockjaw'.
- Generalized rigidity of facial muscles, leading to the classical risus sardonius or clenched teeth expression.
- Rigidity of body musculature, leading to neck retraction and spinal extension.
- Reflex spasms are painful spasms elicited by stimuli such as pressure or noise. These usually occur 1–3 days after the initial symptoms and are potentially very dangerous, as they may endanger respiration and precipitate cardiorespiratory collapse.
- Convulsive seizures.
- Autonomic dysfunction with both sympathetic (sweating, hypertension, tachycardia, dysrhythmias, hyperpyrexia) and parasympathetic (bradycardia, asystole) involvement.

Causes

Exotoxin blocks inhibitory pathways within the CNS.

Assessment of severity

Rapidly progressing features and the onset of spasms signify worse disease and prognosis.

Management

- **Assess severity:** in severe spasms/respiratory failure, ventilation will be required. Otherwise patients should be nursed in a quiet, dark room (to reduce reflex spasms) under close observation. Sedation with diazepam may be necessary, but beware of respiratory depression.
- **General management:** as discussed under  Neuromuscular respiratory failure: assessment, pp. 440–1.
- **Specific treatment:** human hyperimmune globulin 3000–10 000U IV or IM should be given to neutralize the circulating toxin. This will not ameliorate existing symptoms but will prevent further binding of the toxin to CNS. Penicillin IV (1.2g qds), or alternatively tetracycline 500mg qds, should be prescribed to treat *C. tetani*.
- **Wound care and debridement as appropriate:** swabs should be sent for culture but often do not grow the organism.
- **Prophylaxis in patients who have previously been immunized:** for any wound, give a booster dose of tetanus toxoid if the patient has not received a booster in the last 10 years. If the wound appears dirty and infected, or the patient has never been immunized/cannot recall/unable to give a history, give human antitoxin (250U IM), in addition to the toxoid.



Glasgow Coma Scale (GCS)

Developed to assess the depth and duration of impaired consciousness in a standard fashion. The total is out of 15 (see Table 6.9); the worst possible score is 3 (which can even be compatible with death). The scale has a high rate of inter-observer agreement, and the GCS score is one useful way of monitoring conscious level.

Eye opening

- If spontaneous, indicates brainstem arousal mechanisms are probably intact, but the patient need not be aware of their surroundings.
- Eye opening to speech is not necessarily a response to a verbal command to open the eyes; any verbal approach, e.g. calling the name of the patient, may elicit this.
- Eye opening to pain is best tested by using a stimulus in the limbs, because supraorbital or styloid process pressure can lead to grimacing with eye closure.

Verbal responsiveness

- An orientated patient knows who they are, where they are, and why they are there; they can recollect the month and year.
- A confused patient will converse, but their responses indicate varying degrees of disorientation and confusion.
- An individual with inappropriate speech cannot sustain a conversation; their utterances are exclamatory or random and may consist of shouting or swearing.
- Incomprehensible speech does not consist of any recognizable words but involves moaning and groaning.

Motor response

(See Fig. 6.3.)

- Patients who obey commands show the best possible motor response, but be careful not to misinterpret postural adjustments or the grasp reflex.
- If there is no response to command, a painful stimulus may be applied initially by applying pressure to the fingernail bed. If this elicits flexion at the elbow, pressure may be applied to the styloid process, supraorbital ridge, and trunk to see if there is localization.
- If pain at the nail bed elicits a rapid withdrawal, with flexion of the elbow and abduction at the shoulder, it is scored 4.
- If instead it produces a slower flexion of the elbow, with adduction at the shoulder, it is considered an *abnormal flexion response* (sometimes called *decorticate posturing*).
- If pain elicits extension of the elbow, adduction, and internal rotation of the shoulder, with pronation of the forearm, this is noted as an *extensor response* (sometimes called *decerebrate posturing*).

Prognosis

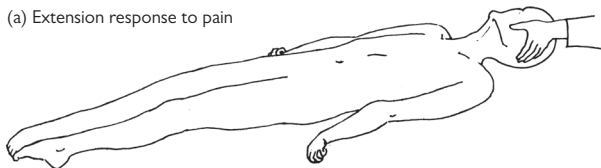
The GCS is a valuable tool in predicting likely outcome from coma, *but it has limitations* and should not be the only factor used to assess prognosis. Patients with GCS scores of 3–8 generally have far worse prognoses than those with scores of >8. But the cause of coma is also an important predictor, e.g. metabolic coma (especially due to drug intoxication) generally has a better outlook than other causes, irrespective of the GCS score.

Table 6.9 GCS*

Eye opening	
Spontaneously	4
To speech	3
To painful stimulus	2
No response	1
Best verbal response	
Orientated	5
Disorientated	4
Inappropriate words	3
Incomprehensible sounds	2
No response	1
Best motor response	
Obeys verbal commands	6
Localizes painful stimuli	5
Withdrawal to pain	4
Flexion to pain	3
Extension to pain	2
No response	1

* Adapted from *The Lancet*, 304(7872), Graham Teasdale and Bryan Jennett, 'Assessment of coma and impaired consciousness: a practical scale', pp. 81–4, Copyright (1974), with permission from Elsevier.

(a) Extension response to pain



(b) Flexion response to pain

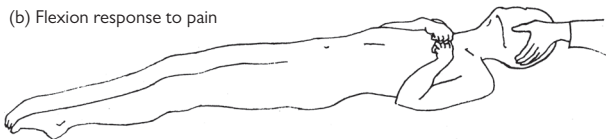


Fig. 6.3 Posturing in coma.

Examination of brainstem function 1

Assessment of brainstem function is vital to the management of coma (➡ Coma: assessment, pp. 348–9), raised ICP (➡ Raised intracranial pressure, pp. 388–90), brainstem strokes (➡ Brainstem stroke, pp. 426–7), and brain death (➡ Brain death, p. 468). It is not necessary to have a detailed knowledge of brainstem anatomy. Some simple observations reveal a great deal about function at different levels of the brainstem.

Examination of the eyes

- *Pupillary reactions*: the size of the pupils and their reactions to bright light should be assessed. This tests the pathway from each eye (IInd cranial nerve) through the superior colliculus (midbrain), its connection to the nearby Edinger–Westphal IIIrd nerve nucleus (also in the midbrain), and the efferent parasympathetic outflow of the IIIrd nerve. The pupillary reflex is consensual, so light in one eye should elicit constriction of both pupils. Thus, observations of the pupillary response can interrogate brainstem function at the level of the midbrain.
- *Corneal reflex*: tests the integrity of the afferent pathway (Vth nerve) through to the efferent pathway (VIth nerve). The corneal reflex is also a consensual reflex. This reflex allows one to interrogate brainstem function at the level of the pons.
- *Resting eye position*: may give a useful clue to asymmetric brainstem dysfunction. If the eyes are dysconjugate, there must be a disorder of the nuclei of the IIIrd, IVth, or VIth nerves, their connections, or the nerves themselves. Note the IIIrd and IVth nuclei are located in the midbrain, whereas the VIth nucleus is located in the pons.
- *Spontaneous eye movements*: if there are spontaneous fast (saccadic) horizontal and vertical conjugate eye movements, the brainstem mechanism for generating saccades is intact and there is no need to test for the oculocephalic or oculovestibular response because:
 - Horizontal saccades require the integrity of the paramedian pontine reticular formation (pons), the IIIrd nerve nucleus, the VIth nerve nucleus, and the medial longitudinal fasciculus connecting these.
 - Vertical saccades require the dorsal midbrain to be intact.
 - Dysconjugate eye movements raise the possibility of unilateral damage to brainstem oculomotor nuclei, their connections, or cranial nerves innervating the extraocular muscles. In this case, the resting position of the eyes may also be dysconjugate.
 - A number of oculomotor signs associated with brainstem dysfunction have been identified; none are absolutely specific, but they may provide useful clues to site of lesion.³²

- *Oculocephalic response*: the 'doll's head manoeuvre' (↻ Oculocephalic and oculovestibular responses, pp. 466–7) should be performed only if cervical injury has been excluded. Both it and caloric stimulation assess the integrity of the vestibulo-ocular reflex (VOR), which is a three-neuron arc from the semicircular canals via the vestibular nuclei to the IIIrd and VIth nerve nuclei.
- *Oculovestibular response*: caloric stimulation (↻ Oculocephalic and oculovestibular responses, pp. 466–7).

References

32. Lewis SL, Topel JL (1992). Coma. In: Weiner WJ, ed. *Emergent and Urgent Neurology*. Lippincott, Philadelphia, PA; pp. 1–25.

Examination of brainstem function 2

The swallowing reflex

This may be tested by injecting 10mL of water in a syringe into the mouth of the patient. Reflex swallowing requires, among other things, that the swallowing centre in the reticular formation of the medulla, very close to the solitary nucleus, is intact. Not often tested.

Respiratory pattern

(See Fig. 6.4.)

- This is sometimes useful in localization but often is not.
- *Central neurogenic hyperventilation*, for example, has no localization value. It is rapid, regular deep continuous breathing at 25/min, which is not produced by acidosis or hypoxaemia. Its usefulness is that increasing the regularity of this pattern signifies increasing the depth of coma and worsening prognosis.
- *Apneustic breathing* (prolonged inspiration, followed by a period of apnoea), on the other hand, implies damage to the pons, as does *cluster breathing* (closely grouped respirations, followed by a period of apnoea). Damage to the medullary respiratory centres is suggested by *ataxic breathing* and *gasping breathing* (Biot's respirations). The former are characterized by a chaotic pattern of respiration; the latter consists of gasps, followed by apnoeic periods of variable duration. Both are usually soon followed by respiratory arrest.
- Shallow, slow breathing may be due to medullary depression caused by drugs, e.g. opiates. *Cheyne–Stokes respiration* may be caused by bilateral deep hemispheric and basal ganglia damage but is more usually due to non-neural causes, e.g. primary cardiovascular or respiratory dysfunction.
- *Long tract signs*: finally, structural damage to the brainstem may produce long tract signs with dysfunction of descending pyramidal/extrapyramidal tracts or ascending sensory pathways. There may be 'crossed signs' because of decussation of pathways within the brainstem.

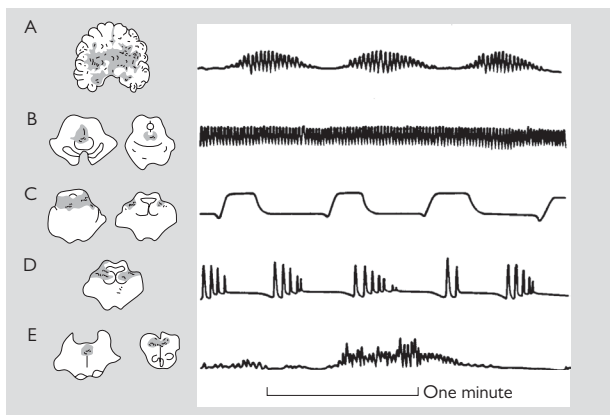


Fig. 6.4 Abnormal respiratory patterns associated with pathologic lesions (shaded areas) at various levels of the brain. (A) Cheyne-Stokes respiration. (B) Central neurogenic hyperventilation. (C) Apneusis. (D) Cluster breathing. (E) Ataxic breathing.

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Examination of brainstem function 3

Signs of brain shift

Raised ICP may produce a number of distinct progressive brainstem syndromes associated with brain shift:³³

- 1 Central herniation syndrome.
- 2 Lateral (uncal) herniation syndrome.
- 3 False localizing signs.
- 4 Tonsillar herniation.

Assessment involves:

- Observation of respiratory pattern.
- Pupillary reaction.
- Oculocephalic/oculovestibular response.
- Motor response at rest or to pain (➡ Glasgow Coma Scale (GCS), p. 458).

Central herniation syndrome

- Vertical displacement of the brainstem due to a supratentorial mass.
- The first sign is not of brainstem, but rather *diencephalic* impairment. The patient becomes less alert and there may be Cheyne–Stokes breathing. The pupils are small (perhaps due to hypothalamic sympathetic dysfunction) but reactive. There may initially have been unilateral hemiplegia due to the supratentorial mass. Characteristically in the early diencephalic stage, paratonic resistance (*gegenhalten*) develops in the contralateral limbs and both plantar responses become extensor. Eventually there is a decorticate response to pain (➡ Glasgow Coma Scale (GCS), p. 458).
- *Midbrain–upper pontine* dysfunction becomes evident with fluctuations in temperature, onset of central neurogenic hyperventilation, apneustic or cluster breathing (➡ Examination of brainstem function 2, p. 462), unreactive pupils which are ‘mid-position’ and often irregular in shape, loss of vertical eye movements (which may be tested with the doll’s head manoeuvre), and increasing difficulty in eliciting horizontal oculocephalic and oculovestibular responses which may become dysconjugate (➡ Oculocephalic and oculovestibular responses, pp. 466–7). Motor responses progress from decorticate (flexor) rigidity to decerebrate (extensor) rigidity in response to pain (➡ Glasgow Coma Scale (GCS), p. 458).
- *Lower pontine–upper medullary* compromise is revealed by often ataxic breathing, fixed mid-position pupils, and failure to elicit oculocephalic and oculovestibular responses. The patient is flaccid at rest; painful stimuli may not elicit any motor response, except occasional flexor responses in the lower limbs.
- *Medullary dysfunction* is terminal. Breathing is ataxic or gasping. The *pulse rate may decrease and BP increase* (Cushing response). After a few gasps, breathing stops and pupils often dilate and become fixed.

Lateral (uncal) herniation syndrome

- Due to lesions in the lateral middle fossa or temporal lobe pushing the medial edge of the uncus and hippocampal gyrus over the free lateral edge of the tentorium.
- The first sign is a *unilaterally dilating pupil* (due to compression of the IIIrd nerve at the tentorial hiatus), which is initially sluggish in response to light. This may soon be followed by ptosis and complete IIIrd nerve palsy with a fixed, dilated pupil. Oculocephalic and oculovestibular responses initially reveal only the palsy but are otherwise intact.
- *Midbrain* compression by the herniating uncus may follow rapidly (the diencephalic stage of central herniation is bypassed). The patient becomes progressively less alert and slips into coma. The oculocephalic and oculovestibular responses cannot be elicited. A hemiplegia ipsilateral to the expanding supratentorial lesion (due to the opposite cerebral peduncle being compressed at the tentorial edge) develops and soon progresses to bilateral extensor plantar responses. As compression continues, both pupils become fixed in mid-position and central neurogenic hyperventilation commences.
- The rostrocaudal progression of signs associated with central herniation then follow with decerebrate/extensor rigidity, etc., as already described. Note decorticate/flexor response to pain is not usually seen in uncal herniation because the diencephalic stage is bypassed.

False localizing signs

As they expand, supratentorial lesions may distort intracranial structures and produce signs which appear to help in localizing the lesion but are, in fact, due to traction 'at a distance'. The most common of these involve cranial nerves V–VIII.

Tonsillar herniation

Subtentorial expanding lesions cause herniation of the cerebellar tonsils through the foramen magnum and compress the pons and midbrain directly. A degree of upward herniation through the tentorial hiatus may also occur and lead to compression of the upper midbrain and diencephalon. It may be difficult to distinguish these effects from those produced by supratentorial lesions. One clue is that there is usually a lack of the rostrocaudal sequence of central herniation.

References

33. Posner JB, Saper CB, Schiff ND, Plum F (2007). *Plum and Posner's Diagnosis of Stupor and Coma* (Contemporary Neurology Series), 4th edn. Oxford University Press, New York, NY.

Oculocephalic and oculovestibular responses

Background

Passive rotation of the head, with respect to the trunk, stimulates vestibular and neck receptors. In comatose patients with intact brainstems, this leads to reflexive *slow conjugate* eye movements in the direction opposite to head rotation. The contribution of neck proprioceptors (cervico-ocular reflex) is minimal; the most important reflex pathway in the brainstem extends from the semicircular canals to the oculomotor nuclei (VOR). Ice water irrigation of a semicircular canal 'switches off' its contribution to this pathway and leads to unopposed function of the contralateral semicircular canal. The eyes then deviate towards the irrigated semicircular canal. Both the doll's head manoeuvre and caloric tests check the integrity of the VOR; the latter is more sensitive.

Oculocephalic/doll's head response

- The doll's head manoeuvre should not be attempted if there is any possibility of cervical spine injury.
- The patient's head is first rotated laterally from one side to the other. Vertical movements may be elicited by flexion and extension of the head.
- 'Positive' responses are noted if turning of the head elicits *slow conjugate* deviation of both eyes in the direction opposite to head movement (see Fig. 6.5).
- Because there is much confusion about what constitutes positive or negative responses, it is best simply to describe what you see.

Oculovestibular/caloric response

- Caloric testing should be performed when the oculocephalic response is abnormal or cannot be performed (e.g. spine fracture).
- The head is then raised 30° above supine, and 100mL of ice water is injected into the external auditory meatus using a thin polyethylene catheter.
- A 'positive' response occurs when both eyes move towards the irrigated ear (see Fig. 6.5). This may take up to a minute. Five minutes should elapse before the other ear is tested.

Significance of results

- If the VOR is intact, major brainstem pathology is unlikely.
- If the horizontal VOR is absent, but the vertical one is present, there may be a lesion at the level of the pons.
- If both responses are absent, there is either a major structural brainstem lesion (see Fig. 6.5) or there is a metabolic disturbance depressing brainstem function (e.g. opiates). Check pupil size and response to light; symmetrically reactive pupils suggest metabolic coma. Only a few drugs, such as atropine, hyoscine, and glutethimide, depress brainstem function and produce pupillary abnormalities.

- If dysconjugate eye movements are elicited, a brainstem lesion is likely. Check to see if there is an internuclear ophthalmoplegia.
- It may not be possible to elicit a VOR using the doll's head manoeuvre because the patient has fast, roving saccadic eye movements. These suggest an intact brainstem.

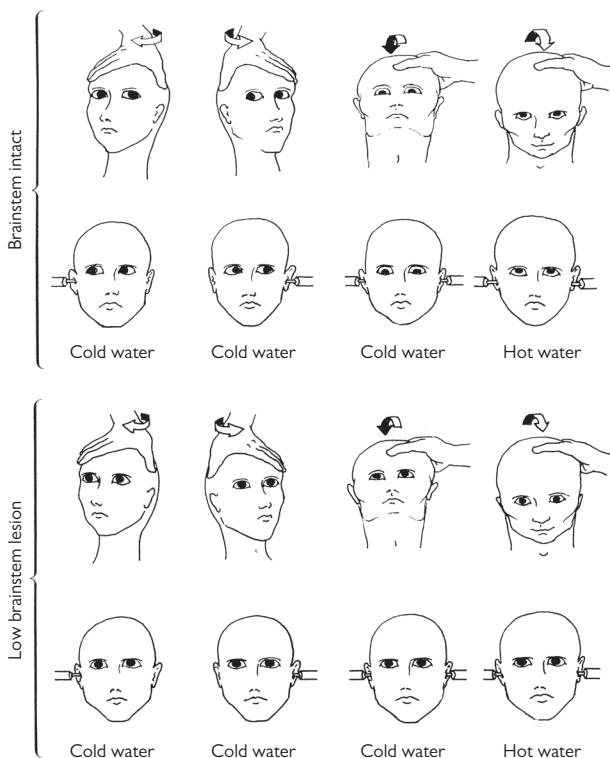


Fig. 6.5 Oculocephalic responses.

Brain death

This is irreversible loss of the capacity for consciousness combined with irreversible loss of the capacity to breathe. Without the brainstem, both these functions are lost. But patients with severe, irreversible brain damage who have no brainstem function may survive for weeks or months, provided they have a normal circulation and are mechanically ventilated. Criteria for brain death have therefore been developed. It has been shown that patients who fulfil these, even if they are ventilated, will eventually develop cardiovascular collapse.

Preconditions

- There must be no doubt that the patient has irremediable structural brain damage which has been diagnosed with certainty. Usually, this is a head injury or an intracranial haemorrhage, but it may be anoxia post-cardiac arrest when it is not always possible immediately to be certain that brain damage is irremediable.
- The patient must be in apnoeic coma (unresponsive to noxious stimuli and on a mechanical ventilator), with no spontaneous respiratory effort.
- There must be no possibility of drug intoxication and no paralysing or anaesthetic drugs should have been administered recently. Hypothermia must be excluded as a cause of coma and the core temperature (rectal or external auditory meatus) should be $>35^{\circ}\text{C}$.
- There must be no significant metabolic, endocrine, or electrolyte disturbance, either causing or contributing to coma.

Tests for confirming brain death

All brainstem reflexes must be absent

- Pupils fixed and unresponsive to bright light (they need not be dilated). Paralytic eye drops, ocular injury, and lesions of the IInd/IIIrd cranial nerves may pose problems in this assessment.
- Absent corneal reflexes.
- Absent VORs on irrigation of each ear, in turn, with 20mL of ice-cold water.
- No motor response within the cranial nerve distribution (eye, face, head) elicited by stimulation of any somatic area (nail bed, supraorbital, and Achilles tendon pressure on each side). Purely spinal reflexes, e.g. deep tendon reflexes, may be retained.
- No reflex response to touching the pharynx (gag reflex) nor to a suction catheter passed into the trachea (cough reflex).

Apnoea

- No respiratory movements when the ventilator is disconnected and $P_a\text{CO}_2$ reaches 6.65kPa. (In order to avoid anoxia during this procedure, the patient should be ventilated with 100% O_2 for 10min beforehand; during disconnection, 6L/min 100% O_2 should be delivered via a tracheal catheter. If just prior to disconnection, $P_a\text{CO}_2$ is $<3.5\text{kPa}$, give 5% CO_2 in O_2 via the ventilator until this level is reached, usually within 5min.)

The tests must be performed by two experienced clinicians, and all the above should be repeated after an interval which depends upon the clinical context.

NB Consider the patient a potential organ donor. Discuss with relatives, and contact the transplant coordinator for your area. Alternatively, contact the duty officer for the UK Transplant Support Service (tel: 01179 757575).

Infectious diseases

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Fever in a returning traveller 1

Assessment

- It is important to obtain a very accurate history of what countries were visited, what areas within those countries, and the activities of the individual while they were there (i.e. visits to rural areas or urban travel only, camping versus luxury hotels, contact with animals or with unwell humans, rafting/trekking/swimming/caving, etc.), together with dates in relation to the onset of illness, what drugs (such as antimalarial prophylaxis) were taken, and what were forgotten.
- Do not forget that, although the patient has travelled, they may have common infections such as pneumonia or pyelonephritis. Some infections have a prolonged incubation and may not have been acquired during the most recent trip, so a travel history encompassing the last 6–12 months is important.

Initial investigations

(See Box 7.1.)

Management

- The epidemiology and drug resistance patterns of many tropical pathogens are constantly changing, and expert advice can be easily obtained from regional ID units. The telephone numbers of the schools of tropical medicine are given under ➡ Useful contacts, p. 914.
- *Patients should only be sent home if there is no evidence of a serious bacterial infection, they are afebrile, and a malaria film is negative. A single malaria film does not exclude malaria, and the patient must be reviewed immediately if further fever occurs.*
- **Isolation.** If there is a history of travel to regions with a risk of viral haemorrhagic fever (VHF) (➡ Viral haemorrhagic fevers, p. 492) in the last 21 days (particularly rural Nigeria, Sierra Leone, Guinea, or Liberia) and the patient is febrile, immediately isolate. The patient should be assessed according to national guidance (see link in Box 7.1). Discuss the case *immediately* with the regional ID unit. Only a malaria film and other immediately relevant blood tests should be performed after discussion with the on-site labs. If confirmed as viral haemorrhagic, transfer to a supra-regional high-security ID unit is mandated. If malaria is diagnosed, management can proceed, as described under ➡ Malaria: management, p. 477. All other patients should be nursed in a side room until a diagnosis is established.
- Clinical *rabies* is rare in the UK but should be considered in travellers with severe encephalitis coming from a rabies-endemic area or those with bat bites both in the UK or abroad. A more common problem is that patients quite frequently present having suffered an animal bite when travelling in an endemic area. Post-bite prophylaxis can prevent rabies in virtually all cases (➡ Non-human mammalian bites, p. 496).

- TB should be considered when evaluating all patients, particularly those brought up, or resident for a long time, in eastern Europe, the Indian subcontinent, South East Asia, or Africa. TB is a frequent presenting illness in advanced HIV infection, especially in sub-Saharan African patients, and may be extra-pulmonary (e.g. TB meningitis, miliary TB, abdominal TB). All patients with TB should be offered HIV testing. Consider drug-resistant TB, especially if the patient was previously treated for TB or has been in prison in eastern Europe.

Box 7.1 Investigations for febrile travellers

- *FBC* Look for anaemia (malaria, hookworm, malabsorption, leishmaniasis), leucocytosis (bacterial infections, amoebic liver abscess) or leucopenia (malaria, typhoid fever, dengue fever, acute HIV seroconversion), eosinophilia (helminth/worm infection), and thrombocytopenia (malaria, typhoid fever, dengue fever).
- *Blood films* Thick and thin films should be examined by a haematologist for malaria. Malaria antigen dipstick tests on blood are now commercially available, are quick, and require minimal training.
- *U&Es* Renal failure may be seen with *Plasmodium falciparum*, VHFs (☞ Viral haemorrhagic fevers, p. 492), and bacterial sepsis.
- *LFTs* Jaundice and abnormal liver function are seen with hepatitis A–E, malaria, leptospirosis, yellow fever, typhoid fever, liver abscesses, and many others.
- *Clotting studies* Deranged with VHFs (☞ Viral haemorrhagic fevers, p. 492), *P. falciparum*, bacterial sepsis, and hepatitis.
- *Blood cultures* Mandatory for all febrile patients.
- *Urinalysis* For leucocytes, nitrites, blood, and protein, and a specimen for culture.
- *CXR* For pneumonia. Raised right hemidiaphragm in amoebic liver abscess.
- *Other investigations to consider* Serology (hepatitis A, B, C, and E), CXR, USS abdomen, sputum MC&S.

Note that if the clinical presentation suggests a risk of VHF, communication with the laboratories must entail a warning to ensure appropriate precautions are taken (see Public Health England's risk assessment guideline at <https://www.gov.uk/government/publications/viral-haemorrhagic-fever-algorithm-and-guidance-on-management-of-patients>).

Fever in a returning traveller 2

(See Table 7.1.)

Table 7.1 Presenting features in travellers with a fever	
Presenting feature	Diagnosis to consider
Jaundice	Malaria, hepatitis A, B, C, and E, leptospirosis, yellow fever, typhoid fever, liver abscess
Splenomegaly	Malaria, leishmaniasis
Hepatosplenomegaly	Malaria, schistosomiasis, typhoid fever, brucellosis, leishmaniasis
Diarrhoea and vomiting	<i>Escherichia coli</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter</i> , <i>Giardia</i> , <i>Entamoeba histolytica</i> , cholera, <i>Vibrio parahaemolyticus</i> , viral gastroenteritis
Skin lesions	Erythema nodosum (TB, leprosy, fungi, post-streptococcal infection) (see Fig. 7.1) Burrows (scabies) Painful nodule with punctum (cutaneous myiasis, i.e. maggots—these need removal) Dermatitis (onchocerciasis) Ulcers (syphilis, leprosy, leishmaniasis) Scabs, eschars (typhus, anthrax) Erythema chronica migrans (Lyme disease)
Abdominal pain	With diarrhoea in dysentery, perforation of bowel (typhoid fever, dysentery), cholecystitis, and cholangitis
Haematuria	VHFs (🔴 Viral haemorrhagic fevers, p. 492), schistosomiasis, haemoglobinuria in <i>P. falciparum</i>
Meningism/confusion	Bacterial, viral, fungal, or parasitic meningitis or meningoencephalitis
Bleeding tendency	Meningococcal septicaemia, haemorrhagic fevers, leptospirosis
RUQ pain ,intercostal tenderness ± right pleural effusion	Amoebic liver abscess or hydatid liver cyst
Pleural effusion	TB, liver abscess, parapneumonic effusion, empyema

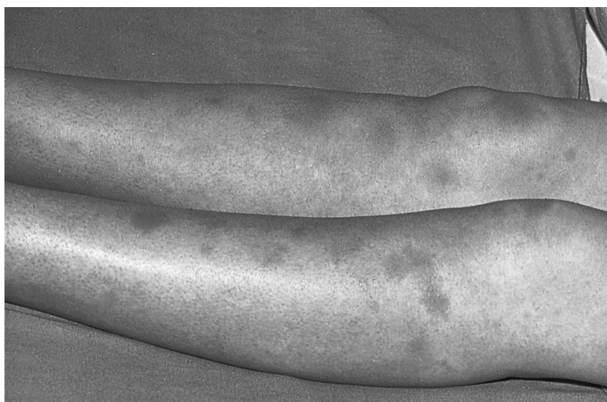


Fig. 7.1 Erythema nodosum. The lesions can be very faint but are indurated and painful on palpation. Reproduced from MacKie R. *Clinical Dermatology*, 2003, with permission from Oxford University Press.

Malaria: assessment

There are ~2000 cases of malaria in the UK each year, with 1% mortality. The 2016 UK national guidelines can be accessed at: [https://www.journalofinfection.com/article/S0163-4453\(16\)00047-5/pdf](https://www.journalofinfection.com/article/S0163-4453(16)00047-5/pdf)

Organism

- *P. falciparum* is the causative agent of the most severe and potentially fatal form of malaria.
- *P. vivax* and *P. ovale* may cause chronic, recurrent disease, and there is emerging evidence that *P. vivax* can cause more severe presentations than previously thought. *P. malariae* rarely causes life-threatening disease and can be managed as an outpatient.
- Different species can be distinguished by their morphology on a blood film, but this needs expert interpretation. Malaria antigen blood dipstick testing can differentiate reliably between *P. falciparum* and *P. vivax*. Mixed infections can occur. If in doubt, therapy should be directed against *P. falciparum*.

Symptoms

- Incubation period from 6 days minimum up to 3 months (usually within 1 month) for *P. falciparum*, up to 2 years for *P. vivax* and *P. ovale*, and up to 20 years for *P. malariae*.
- High fever, chills, and rigors, followed by sweating. Alternate-day fever is described, but many patients do not exhibit this.
- Headache is a very common symptom. If associated with impairment in consciousness, behavioural change, or seizure activity, consider hypoglycaemia. Cerebral malaria is defined as unrousable coma (GCS score ≤ 9). Retinal haemorrhages, drowsiness, and other neurological signs may indicate lesser cerebral involvement, which may progress.
- Generalized flu-like symptoms, malaise, and myalgia.
- Abdominal symptoms: anorexia, pain, vomiting, and diarrhoea (especially in children).

Examination

- No specific features.
- Pyrexia in most, but not all, cases, often up to 40°C during paroxysms.
- Splenomegaly.
- Anaemia and jaundice.
- Indications of severity (see Box 7.2).

Box 7.2 Indicators of severity in *P. falciparum* malaria

- Impaired consciousness or seizures.
- Renal impairment (oliguria $<0.4\text{mL/kg}$ bodyweight per hour or creatinine $>265\text{micromol/L}$).
- Acidosis ($\text{pH} <7.3$).
- Hypoglycaemia (glucose $<2.2\text{mmol/L}$).
- Pulmonary oedema or ARDS.
- Hb $<80\text{g/L}$.
- Spontaneous bleeding/DIC.
- Shock (BP $<90/60\text{mmHg}$).
- Haemoglobinuria [without glucose-6-phosphate dehydrogenase (G6PD) deficiency].
- Severe parasitaemia ($>2\%$).

Malaria: investigations

All patients should have FBC, U&Es, creatinine, LFTs, and blood glucose. In ill patients, blood gases, blood cultures, lactate, and clotting studies should be performed. Urine dipstick/MC&S, stool culture, CXR, and LP may be appropriate.

- **FBC:** anaemia, non-immune haemolysis, leucopenia, and thrombocytopenia suggest *P. falciparum*.
- **Blood films:** repeated blood samples over several hours should be examined by an experienced individual if the patient is unwell and malaria was not found on the initial blood film. At least three films should be examined (separated by at least 12h). A malaria antigen blood dipstick test for *P. falciparum* should also be performed (for *P. falciparum*, this is as sensitive as a blood film read by an experienced microscopist but is less sensitive for *P. vivax* and *P. ovale*). If in doubt, seek advice from an expert urgently and send the films to a reference laboratory for a definitive opinion. Thin films make speciation easier and are used to calculate the percentage parasitaemia.
- **Parasitaemia:** severe—>2% parasitaemia or schizonts on film.
- **G6PD status:** some treatment options cause haemolysis in G6PD deficiency.
- **Glucose:** hypoglycaemia may occur with *P. falciparum* or IV quinine therapy, especially during pregnancy.
- **U&Es, LFTs:** ARF and haemoglobinuria may occur in severe *P. falciparum*. Elevated unconjugated bilirubin, AST, and LDH reflect haemolysis.
- **Blood cultures:** even if malaria is confirmed. Other infections, such as Gram -ve septicaemia, may also be present (termed 'algid' malaria).
- **Head CT scan and LP:** may be required in suspected cerebral malaria to exclude other pathologies.
- **ABG:** metabolic acidosis (pH <7.3) indicates severe malaria.

Malaria: management

General measures

(See Box 7.3.)

- Malaria should be managed in consultation with an ID specialist.
- All cases of *P. falciparum* malaria should be admitted to hospital.
- Lower fever with tepid sponging and paracetamol.
- If severe malaria or cerebral malaria, admit to HDU/ITU.
- Fits can be controlled with diazepam.
- In severe cases, catheterize the bladder to monitor urine output, and insert a CVP line to help manage fluid balance, as ARDS can easily be precipitated in these patients. Renal support may be required.
- 2-hourly blood glucose estimations. Regular temperature, pulse, and respiratory rate (TPR), BP, and urine output.
- Pre-treatment ECG required when IV quinine is being used (causes QT prolongation), but do not delay giving therapy.
- In severe cases, repeat blood films at least twice daily until parasitaemia is clearly falling, and then perform daily. Daily U&Es, FBC, and LFTs.
- Thrombocytopenia is usual and rarely needs support, unless platelet count $<20 \times 10^9/L$ or bleeding.
- Discuss any severe or complicated malaria with an ID unit early.
P. falciparum acquired on the Thai borders and in neighbouring countries may be drug-resistant and need treatment with less commonly available antimalarials.

Malaria: antimalarial therapy

For advice in the UK, phone the Imported Fever Service on 0844 7788990 (treatment); or for travel prophylaxis, phone the National Travel Health Network and Centre (NaTHNaC) on 0845 6026712. See Box 7.3 for key points in the management of malaria.

P. falciparum

Uncomplicated, non-severe P. falciparum in adults

- Artemether-lumefantrine: if weight >35kg, four tablets stat, then four tablets at 8, 24, 36, 48, and 60h.
- Atovaquone/proguanil (Malarone®) is licensed for the treatment of non-severe *P. falciparum*. For adults, four tablets od for 3 days.
- Quinine 600mg tds PO, reduced to bd if the patient develops severe cinchonism (nausea, tinnitus, deafness). For 5–7 days until afebrile and blood film negative plus either doxycycline 100mg bd PO or (particularly if pregnant or <12 years old) clindamycin 450mg tds PO for 7 days.
- Parenteral treatment of malaria should be given if there is >2% parasitaemia, the patient is pregnant, or in patients unable to swallow tablets.

Complicated or severe P. falciparum in adults

- Discuss with an ID physician and ITU at the earliest opportunity.
- Artesunate regimen: 2.4mg/kg given as an IV injection stat, repeated at 12h, 24h, and then daily thereafter. After completion of a minimum of 24h therapy (maximum 5 days), a full course of an oral artemisinin-based combination therapy (ACT) should be taken when the patient can tolerate oral medication.
- Where artesunate cannot be obtained rapidly, use quinine dihydrochloride IV 20mg/kg in 5% glucose or glucose-saline over 4h (maximum dose 1.4g). After 8h, the patient should be treated with quinine at 10mg/kg infused over 4h (maximum dose 0.7g), repeated every 8h for 48h. Watch carefully for toxicity (QT prolongation and hypoglycaemia). Consider change to an oral regime at 48h with quinine 600mg tds to complete 5–7 days of treatment.
- Quinine treatment should be accompanied by a second drug (doxycycline 100mg bd or clindamycin 450mg tds) for 7 days.
- Chloroquine resistance is widespread. It is not used to treat *P. falciparum* malaria.

Intensive care management of severe or complicated malaria

- Careful management of fluid balance to optimize O₂ delivery and reduce acidosis.
- Monitoring of CVP to prevent pulmonary oedema and ARDS.
- Regular blood glucose monitoring to detect and prevent hypoglycaemia.
- Consider broad-spectrum antibiotics if evidence of shock or concomitant bacterial infection.
- Haemofiltration for renal failure or control of acidosis or fluid/electrolyte imbalance.
- Consider medication to control seizures.

- Current opinion is that exchange transfusion is no longer indicated in severe malaria.
- Steroids are not recommended for cerebral malaria.
- Repeat daily blood films until trophozoites cleared (i.e. undetectable parasitaemia).

P. vivax*, *P. ovale*, and *P. malariae

- *Admission*: if the diagnosis is clear and the patient is stable, admission may not be necessary; however, many will require admission for short stay. General measures are as described earlier.
- *Acute therapy*: chloroquine remains the drug of choice, with only very limited resistance reported for *P. vivax* (predominantly in Papua New Guinea, East Timor, and Indonesia). Give chloroquine: 600mg (base) stat, followed by 300mg 6h later and 300mg daily for 2 days.
- *Prevention of relapse*: persistent hepatic hypnozoites occur with *P. vivax* and *P. ovale* and can cause relapse. Treatment is with primaquine 15mg daily for 14 days (higher doses of 30mg daily may be warranted on specialist advice) after completion of chloroquine treatment. Check G6PD levels before giving primaquine, as it induces severe haemolysis in these patients—seek advice.
- *Patient advice*: avoid contact sports for 1 month because of the risk of splenic rupture.

Box 7.3 Management key points: malaria

- Admit to ITU if severe or cerebral malaria.
- Monitor blood glucose, temperature, HR, BP, urine output, and fluid balance.
- Discuss with the ID unit. Contact a malaria expert for advice on the best regimen for the country of origin:
 - *P. falciparum*: artesunate (IV if severe) or quinine + doxycycline (or clindamycin) or Malarone® or Riamet®.
 - *P. malariae*: chloroquine.
 - *P. vivax* and *P. ovale*: chloroquine + primaquine (check G6PD levels before giving primaquine).
- Repeat blood films, daily FBC, U&Es, and LFTs.
- Other: lower fever with tepid sponging and paracetamol. Control fits with diazepam. Renal support may be required. Thrombocytopenia is usual and rarely needs support, unless platelet count $<20 \times 10^9/L$ or bleeding.

Infections presenting with fever and rash

(See Table 7.2.)

Table 7.2 Rashes: features of the common childhood exanthems						
Infection	Morphology	Distribution	Incubation	Infectivity	Associated features	Complications
Varicella (chickenpox)	Clear vesicles on erythematous base (5–12mm), evolving into pustules that burst and crust	Lesions occur in crops, start on trunk, and spread peripherally. Mucosal lesions common	10–21 days	4 days before rash to 5 days after last lesion scabs	Pyrexia 1–2 days, flu-like prodrome	Bacterial infection Varicella pneumonia Encephalitis Reactivates as herpes zoster
Measles	Maculopapular, morbilliform	Starts on head and neck, spreading peripherally	10–14 days	A few days before until up to 18 days after rash onset	Coryza, conjunctivitis, cough, lymphadenopathy, Koplik's spots in late prodrome	Otitis media, bacterial pneumonia, measles pneumonia, encephalitis (1:1000), deafness, subacute sclerosing panencephalitis (SSPE)
Rubella (German measles)	Pink macular	Progresses from trunk over 2–4 days, may be very mild or absent	14–21 days	1 week before to 4 days after rash onset	Lymphadenopathy, especially suboccipital	Arthritis in adults Encephalitis rare
Parvovirus (slapped cheek, erythema infectiosum, fifth disease)	Facial erythema in children. Macular or maculopapular, morbilliform or annular	Facial rash in children (slapped cheek) Generalized in adults	5–10 days	Probably 10 days before rash until onset	Lymphadenopathy, arthralgia	Arthritis in adults Fetal loss in pregnancy (hydrops) Anaemia in patients with haemoglobinopathies Chronic infection in immunocompromised

Primary varicella infection (chickenpox)

Chickenpox is an acute infectious disease caused by VZV, usually seen in children <10 years. Reactivation of previous infection can cause shingles (herpes zoster). Chickenpox is highly contagious—infects >90% of those in contact. Incubation period is 10–21 days. The classical rash is described in Table 7.1. Atypical presentations may occur in the immunocompromised host who may have fulminant cutaneous involvement with haemorrhagic chickenpox or conversely can develop systemic involvement with minimal rash.

Complications

Systemic complications are rare in the immunocompetent child, but more frequent in adults and the immunocompromised. In the UK, chickenpox is responsible for about 20 deaths per year in otherwise healthy adults.

- *Secondary bacterial infections*: most frequent complication, 20–50% of hospitalized adults, and responsible for ~50% of chickenpox-associated deaths. Super-infections with group A streptococcal septicaemia in children and staphylococcal skin infections (including toxic shock syndrome) or bacterial pneumonia predominate.
- *Viral pneumonia*: ~1:400 adult cases, with 20% mortality. More common in smokers. Characterized by cough, breathlessness, and hypoxia, with diffuse pneumonitis on CXR.
- *Hepatitis*: severe hepatitis rare, except in the severely immunocompromised. Modest elevation in transaminases is usual.
- *Encephalitis*: incidence of 0.1% in adults, 20–30% mortality.
- *Cerebellar ataxia*: ~1:4000 cases in children, generally self-limited.
- *Reye's syndrome*: epidemiological association in childhood with concomitant aspirin use.
- *Congenital varicella syndrome*.

Management

Antiviral and antimicrobial therapy

- *Immunocompetent children*: antiviral therapy not indicated. Have a high index of suspicion for bacterial infection if ill enough to require hospitalization.
- *Immunocompetent adult moderately unwell*: within first 24h of the onset of rash may benefit from oral valaciclovir 1g tds or aciclovir 800mg five times per day, with reduction in fever and number of lesions.
- *Immunocompetent adult with evidence of pneumonitis*: IV aciclovir 10mg/kg tds and anti-staphylococcal and anti-streptococcal antibiotic cover (e.g. co-amoxiclav if no allergies).
- *Pregnancy*: aciclovir is not licensed for use in pregnancy but appears to be safe and non-teratogenic. Pregnant women are at risk of severe disease and, if presenting within 24h of onset of rash, the use of aciclovir should be discussed with an expert.
- *Immunocompromised adult or child*: aciclovir indicated in all cases. If mild disease and minimal immunosuppression, oral therapy with 800mg five times per day may be sufficient. In more severe immunosuppression, e.g. post-transplant, or any evidence of dissemination, treat with IV 10mg/kg q8h (adult dose).

Prophylaxis for high-risk susceptible patients

- *Hyperimmune immunoglobulin [also known as varicella-zoster immune globulin (VZIG)]* is effective in preventing or ameliorating varicella when given up to 10 days after exposure. Exposure is defined as >15min in the same room or a face-to-face conversation with a case of chickenpox or uncovered shingles from 2 days before the rash until all lesions are crusted. VZIG should be given to all susceptible (i.e. those without a good history of previous chickenpox, with an absent serum VZV IgG result) immunocompromised individuals as soon as possible after exposure to chickenpox or zoster. VZIG is indicated for VZV IgG-negative pregnant women contacts and should also be given to newborn infants whose mothers have had primary varicella 7 days before to 7 days after the birth. UK national guidance on varicella and other viral rash exposure in pregnancy can be found at [JRC https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/322688/Viral_rash_in_pregnancy_guidance.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/322688/Viral_rash_in_pregnancy_guidance.pdf)
- Prophylactic aciclovir (taken from days 7–14 after exposure) is also effective in certain groups but is not licensed for this indication.
- Two live attenuated vaccines are now available in the UK: Varilrix® and Varivax®. These are not part of the routine childhood immunization programme. They are currently indicated for vaccination of susceptible health-care workers (VZV IgG negative) or for susceptible non-immune adults at risk and others felt to be at risk.
- VZIG supplies are limited and tightly controlled. Your consultant virologist or microbiologist should be contacted in the first instance.

Infection control

Chickenpox is infectious from 48h before the onset of the rash until about 5 days after the onset. Patients should be nursed by immune staff using contact precautions in a neutral- or negative-pressure side room on a ward without immunocompromised patients. Shingles is much less infectious, unless it involves the face or other uncovered part of the body.

Herpes zoster (shingles)

Reactivation from the latent virus in the sensory root ganglia. Risk increases with age and immunodeficiency. Vesicular rash developing in crops in a single or multiple dermatomes, or may be disseminated in the immunocompromised. Up to 20 vesicles are normal in immunocompetent individuals. Suspect immunodeficiency in zoster that is recurrent or affects several dermatomes.

Complications

These are more frequent in immunocompromised patients:

- Bacterial infection.
- Post-herpetic neuralgia.
- Eye complications: keratitis occurs in 10% of patients, with involvement of the trigeminal nerve (ophthalmic zoster). Rarely, there may be retinal necrosis.
- Aseptic meningitis: CSF pleocytosis is common and generally asymptomatic.
- Cerebral angiitis leading to a contralateral hemiparesis.
- Transverse myelitis: mainly in immunocompromised patients.
- Cutaneous dissemination: in excess of 20 vesicles outside of the affected dermatome suggests a high risk of systemic dissemination.
- Systemic dissemination: lung, liver, and brain spread occurs, mainly in immunocompromised patients.

Management

- There should be a low threshold for testing for HIV.
- *Immunocompetent adult*: valaciclovir 1g tds, in preference to aciclovir (800mg five times a day), appears to reduce the duration of post-herpetic neuralgia if given within 48h of onset.
- *Ophthalmic zoster*: stain the cornea with fluorescein to detect keratitis; ophthalmology opinion vital if visual acuity or any evidence of eye involvement. If keratitis present, treat with topical aciclovir or trifluoridine ointment and IV aciclovir or oral valaciclovir or famciclovir.
- *Uncomplicated zoster in immunocompromised*: give antivirals to prevent dissemination. Oral aciclovir, famciclovir, or valaciclovir for patients with mild immunosuppression (e.g. on long-term steroid therapy). IV aciclovir (10mg/kg q8h) for patients with severe immunosuppression.
- *Disseminated zoster*: give IV aciclovir 10mg/kg q8h.

Meningococcal infection: assessment

Meningococcal meningitis and septicaemia are severe systemic infections caused by *Neisseria meningitidis*. ~10% of the population carry *N. meningitidis* in their nose or throat, but few develop invasive disease. Outbreaks are most common in teenagers, young adults, and crowded environments. Meningism is absent in 30% of cases. It is a notifiable disease, necessitating an urgent phone call to Public Health, including out of hours.

Rashes

Purpuric lesions are the hallmark of meningococcal septicaemia, but several different patterns may be seen either separately or together. Furthermore, rash is a late sign, and the absence of a rash should not detract from a possible diagnosis of meningococcal infection.

- *Petechial*: initially 1–2mm discrete lesions, frequently on the trunk, lower body, and conjunctivae. Enlarge with disease progression and correlate with thrombocytopenia and DIC, which are poor prognostic signs.
- *Ecchymoses*: the petechial lesions coalesce and enlarge to form widespread purpura and ecchymoses, particularly on the peripheries.
- *Purpura fulminans*: in extreme cases, entire limbs or sections of the body become purpuric and necrotic due to DIC and vascular occlusion.
- *Maculopapular*: non-purpuric and easily mistaken for a viral rash, occurring early in some patients. May look like flea bites.

Presentation

- *Predominantly septicaemia*: symptoms and signs of septicaemia, shock, and respiratory distress. May progress from first signs to death within a couple of hours. Purpuric rash almost always develops but may be absent at presentation. Patient often not meningitic. Give antibiotics immediately after blood cultures. Call ICU immediately. Do not perform LP or CT scan.
- *Predominantly meningitis*: no shock, no respiratory distress. Neurological signs predominate, and a rash may or may not be present.
- *Bacteraemia without meningitis or sepsis*: non-specific flu-like symptoms ± rash. Positive blood cultures. Rash less often present. May develop focal spread such as septic arthritis and pericarditis.
- *Chronic meningococcaemia*: low-grade fever, purpuric rash, and arthritis, often confused with gonococcaemia. Sepsis and meningitis do not develop, and the illness may last for weeks unless recognized.
- *Recurrent meningococcaemia*: suspect immunocompromise, particularly complement deficiency.

Antibiotics

IV 2g cefotaxime or ceftriaxone (➡ Meningococcal infection: management, p. 488).

Investigations

- *Blood cultures*: immediately. Also take EDTA blood sample for PCR and throat swab. FBC, U&Es, glucose, LFTs, clotting.
- *Brain CT scan*: recent guidelines from the British Infection Association recommend that an LP can be performed without a head CT scan in patients with simple meningitis, i.e. not obviously septicaemic, no focal neurological signs, and no decrease in conscious level. A CT scan should be performed prior to LP in all cases of meningitis with depressed consciousness (GCS score <12 or fluctuating coma score, focal neurology, papilloedema, fits, bradycardia, and hypertension). Give antibiotics before CT scan. *Do not delay treatment. Do not delay resuscitation or transfer of a sick patient to ICU to perform an LP, but if feasible and safe, consider once appropriate care instigated.*
- *LP*: *do not perform in patients with predominantly septicaemia* (may be dangerous if DIC). *Do not delay antibiotics beyond 30min* (see Box 7.4).

Differential diagnosis of purpuric rash and fever

- Gonococcaemia.
- Bacterial septicaemia with DIC.
- Haematologic malignancy with sepsis.
- Henocho-Schönlein purpura.
- In travellers consider:
 - Rocky mountain spotted fever (USA).
 - VHF (🌀) Viral haemorrhagic fevers, p. 492).

Box 7.4 LP findings in meningococcal infections

- Opening pressure: often elevated.
- WBC: elevated in ~100%—median 1200 cells/microlitre, mainly PMNs but may be mixed if partially treated.
- Protein: elevated in 90%.
- Glucose : reduced in 75–80%.
- Gram stain: typically Gram –ve diplococci can be seen.
- Culture: positive in 50–80% of meningitis.
- Antigen testing: positive in 50% and correlates with Gram stain.
- Meningococcal PCR: positive.

Meningococcal infection: management

Antibiotic therapy

(See Box 7.5.)

- Treatment must be started *immediately* if a diagnosis of *predominantly meningococcal septicaemia* is suspected. If the diagnosis is *predominantly meningitis*, perform an LP if no contraindications, but do not delay for >30min before antibiotics are given.
- If called by a GP, then instruct the GP to administer benzylpenicillin 1.2g IM/IV or a third-generation cephalosporin before arranging urgent transfer to hospital.

Treatment

- Cefotaxime 2g qds or ceftriaxone 2g bd.
- If the patient has had definite anaphylaxis or near anaphylaxis to penicillin, then urgent discussion with microbiology or ID experts is indicated. Chloramphenicol 25mg/kg qds (max. 1g qds) may be considered, but advice should be sought.
- If there is a possibility that the patient has pneumococcal meningitis and is severely obtunded, start dexamethasone 0.15mg/kg (to max. 10mg) IV qds for 4 days, with or just before the first dose of antibiotics—this has been shown to reduce morbidity substantially.

Prophylaxis

- Notify the case immediately to the local Consultant in Communicable Disease Control (CCDC).
- The CCDC will advise on antibiotic prophylaxis.
- Close contacts only, i.e. household, kissing contacts, close family, institutional contacts (if from a nursing home), etc. in previous 7–10 days.
- Staff members only if involved in resuscitation or ET intubation and suctioning without a mask on.
- Drug choice: ciprofloxacin 500mg as a single dose is now the prophylactic agent of choice for all age groups; alternatives include rifampicin 600mg bd for 2 days or ceftriaxone 250mg IM stat.

Supportive therapy

- Intensive care monitoring is essential in any shocked patient or if significant impairment of consciousness.
- If shocked, urgent fluid replacement, aided by invasive monitoring, is essential. Supportive care for septic shock is discussed under ➡ Sepsis syndrome and septic shock, pp. 336–7.
- Treatment of DIC is supportive.

Prognosis

- Meningitis without shock: mortality ~10%, neurological sequelae uncommon. Coma is a poor prognostic sign.
- Fulminant meningococcaemia: mortality related to organ failure between 20% and 80%.

Further information is available in the form of a NICE guideline at <https://www.nice.org.uk/guidance/cg102>

Box 7.5 Management key points: meningitis

- Do *not* delay treatment because of investigations.
- If called by a GP, instruct the GP to administer benzylpenicillin or a third-generation cephalosporin before arranging urgent transfer to hospital.
- Give cefotaxime 2g qds or ceftriaxone 2g bd. (If there is a clear history of anaphylaxis to penicillin, chloramphenicol may be used.)
- IV fluids in cases of septic shock.
- Monitor shocked patients or those with reduced GCS score in ITU.
- If pneumococcal meningitis is suspected and the GCS score is reduced, consider IV dexamethasone 0.15mg/kg (max. 10mg) IV qds for 4 days, with or just before the first dose of antibiotics.
- Notify Public Health (CCDC) who will advise on antibiotic prophylaxis for close contacts (all age groups: ciprofloxacin as preferred agent; rifampicin or ceftriaxone as alternatives).

Enteric fever (typhoid)

Enteric fever is a severe systemic infection caused by the bacteria *Salmonella enterica* serovar Typhi and *S. enterica* serovar Paratyphi (see Box 7.6). These are usually acquired outside the UK, following the ingestion of contaminated food and water.

Presentation

- Non-specific symptoms, e.g. anorexia, myalgia, headache, malaise, fever, chills, and sweats, common. Remittent temperature gradually rising during the first week to 40°C, with relative bradycardia.
- Abdominal pain (30–40%), D&V (40–60%), or constipation (10–50%) may all be seen. Acute abdomen occurs in later stages (perforation of bowel). Splenomegaly (40–60%) and hepatomegaly (20–40%).
- Respiratory symptoms common, including sore throat and cough.
- Neurological manifestations, including encephalopathy, coma, meningism, and/or seizures, are seen in 5–10%.
- Rose spots are 2–4mm erythematous maculopapular lesions, blanch with pressure, and occur in crops of ~10 lesions on the upper abdomen, lasting only a few hours. Present in only 10–30% and easily missed.
- A fulminant toxæmic form occurs in about 5–10% of cases, with rapid deterioration in cardiovascular, renal, hepatic, and neurological function. In other patients, onset may be quite insidious. In the first 7–10 days after infection, bacteraemia occurs with seeding into the Peyer's patches of the gut, leading to ulceration and necrosis (weeks 2–3).

Investigations

- *Initial week of illness:* normal Hb, WCC, or elevated liver enzymes. Blood cultures positive in 40–80%. Negative cultures should not therefore exclude the diagnosis.
- *Second to third weeks:* Hb, WCC, and platelets due to bone marrow suppression. Blood cultures become negative, urine and stool cultures become positive. Marrow culture positive. AXRs and imaging are indicated if there is abdominal pain.
- *Serology:* unhelpful at discriminating active infection from past exposure or vaccination.

Complications

All uncommon, with prompt diagnosis and therapy.

- *Toxaemia:* acute complications include hyperpyrexia, renal and hepatic dysfunction, bone marrow failure, and myocarditis.
- *GI:* late complications due to breakdown in Peyer's patches, including GI haemorrhage and perforation.
- *Metastases:* meningitis, endocarditis, osteomyelitis, liver/spleen.
- *Chronic carriage:* 1–3% beyond 1 year.

Management

- *Supportive care*: if toxæmic, admit to ITU. Urinary catheter and CVP line to manage fluid balance. May need renal support.
- *Antibiotics*: multiple drug resistance has become a problem, and ampicillin can no longer be used for empirical treatment. Third-generation cephalosporins (e.g. ceftriaxone 2g IV od) are now the empiric treatment of choice until sensitivities are known; if sensitive, quinolones, e.g. ciprofloxacin, 750mg bd PO for 14 days or 400mg bd IV may be appropriate. Azithromycin is a potential oral alternative if the isolate is quinolone-resistant.
- *Surgery*: is essential for bowel perforation (add metronidazole).
- *Infection control*: notify the case to Public Health. Spread is faecal/oral, and individuals should not prepare food until follow-up stool cultures (off antibiotics) are negative.
- Consider vaccination.

Box 7.6 Epidemiology of enteric fever

- *S. enterica* serovar Typhi and serovar Paratyphi (less severe) have a widespread distribution, including Africa, South America, and the Indian subcontinent.
- Incubation period is 7–21 days, and it is very rare >1 month after return from an endemic area.
- Untreated, mortality is 10–15%; with adequate therapy, mortality is <1% in the UK.
- Relapse rate: 1–7%.
- Chronic carrier state: ↑ incidence in the elderly, immunocompromised, and those with gallstones. Ampicillin or amoxicillin (4–6g/day + probenecid 2g/day) or ciprofloxacin (750mg bd) for 4 weeks will clear 80–90% of patients, falling to 20–50% if the patient has gallstones. Cholecystectomy may eradicate carriage, but not usually indicated if carriage is asymptomatic.

Viral haemorrhagic fevers

VHFs are a group of illnesses caused by several different families of viruses (see Table 7.3). The incubation period is 3–21 days. The range of clinical disease caused by these viruses is marked, but many cause severe life-threatening disease, e.g. Ebola and Marburg viruses. VHFs are endemic in some areas of Africa, South America, and Asia and should be considered in febrile travellers returning from endemic areas.

Many patients with suspected VHFs will turn out to have malaria, but when suspected, their management should always be discussed with an ID specialist.

- Dengue fever is commonly imported into the UK (estimated at 100–150 cases/year) and presents with fever, headache, and rash. Cases of the other haemorrhagic fevers are imported only once every few years.
- Recognition is important not least because Lassa, Ebola, Marburg, and CCHF have been transmitted to health-care workers of patients (including laboratory staff). Discuss suspected cases urgently with specialist high-security ID centres regarding investigations and possible transfer.
- Suspected cases include patients with onset of their fever within 21 days of leaving an endemic area, particularly if a malaria film is negative.
- Limit local blood tests to an absolute minimum if a VHF is suspected (but *always* perform malaria testing).

Table 7.3 Characteristics of some viral haemorrhagic fevers

Disease	Clinical features	Outcome/management
Dengue fever (serotypes I–IV) Tropical/sub-tropical zones, Americas, Caribbean, Oceania, Asia, Africa <i>Transmission:</i> mosquito–man; huge epidemics <i>Incubation:</i> 3–15 days (usually 4–7 days)	High pyrexia, headache, joint pain, maculopapular rash on trunk, WCC, and platelets Dengue haemorrhagic shock in 15–25% cases	Isolation not required Mortality low in non-shock cases Treatment supportive Serological diagnosis (acute and convalescent sera); PCR useful in first 5 days of illness only
Yellow fever Tropical Africa, Central and South America <i>Transmission:</i> mosquito–human <i>Incubation:</i> 3–14 days	Severe cases: headache, myalgia, high fever, and vomiting 3–4 days; 1–2 days later, symptoms return with jaundice, haemorrhage, and renal failure, relative bradycardia, leucopenia, DIC, and abnormal liver function	Standard blood/body fluid isolation, advise staff on vaccination Case fatality: 5–20% Treatment supportive Diagnosis by PCR and serology

Table 7.3 (Contd.)

Disease	Clinical features	Outcome/management
Lassa fever Rural districts of West Africa <i>Transmission:</i> rodent–human–human <i>Incubation:</i> 3–21 days	Fever, pharyngitis, retrosternal pain, proteinuria, headache, joint pain, abdominal pain, and vomiting. Maculopapular rash.	Refer suspected cases to high-security isolation facility <i>Mortality:</i> 1–2%, rising to 15–50% in haemorrhagic cases Diagnosis by PCR and serology
Ebola virus Rural areas of West, Central, and East Africa. <i>Transmission:</i> human–human; possible bat reservoir <i>Incubation:</i> 2–21 days	Haemorrhagic manifestations common 3–4 days after onset Haemorrhagic complications in 20–30% of those admitted	Refer suspected cases to high-security isolation facility. Case fatality: 50% Treatment supportive Diagnosis by PCR and serology
Marburg virus Rural districts of Central and South Africa <i>Transmission:</i> animal (most likely bats)–human–human <i>Incubation:</i> 2–21 days		

Congo–Crimean haemorrhagic fever (CCHF)

CCHF is a serious tick-borne viral disease. It is a zoonosis (disease acquired from animals) and infects a range of domestic and wild animals. CCHF virus is endemic in many countries in Eastern Europe, the Middle East, Africa, and Asia. Outbreaks have recently been recorded in Russia, Turkey, Iran, Kazakhstan, Mauritania, Kosovo, Albania, Pakistan, and South Africa.

Hantavirus

Hantaviruses are rodent-borne, zoonotic (acquired from animals) viruses. They cause two serious infections in humans: 'haemorrhagic fever with renal syndrome' (HFRS) and 'hantavirus pulmonary syndrome' (HPS). There are several different hantaviruses; some are present in Europe and Asia, while others occur in North and South America.

Rickettsial infections

- These present with fever, headache, and rash and should be included in the differential diagnosis of febrile travellers. Recognition is important because rickettsial illnesses have significant mortality if left untreated. Isolation is not necessary. Incubation is about 5–14 days.
- *Rickettsia conorii* and *Rickettsia africae* are probably the two most common of the group to be imported into the UK, usually from Africa, but rickettsiae are widely distributed across the world (see Table 7.4).
- Molecular and direct serological diagnostic techniques are not widely available, so treatment has to be given on clinical suspicion. Serology is not positive until the second week of the illness at the earliest and may take 3–4 weeks to become positive (and may be modified by treatment).
- First-line treatment is with doxycycline 100mg bd PO for up to 7 days (other tetracyclines, chloramphenicol, or quinolones have also been used).

Table 7.4 Rickettsial infections

Disease	Clinical features
Typhus group	
Epidemic typhus: <i>Rickettsia prowazekii</i>	Fever, severe headaches, maculopapular rash on trunk spreading to extremities. Complications include pneumonitis, encephalitis, and myocarditis
Murine typhus: <i>Rickettsia typhi</i>	<i>R. typhi</i> less severe than <i>R. prowazekii</i>
Spotted fever group	
Boutonneuse fever: <i>R. conorii</i>	Fever, severe headache, eschar (black scab with surrounding erythema) at site of bite, sparse papular rash
African tick typhus: <i>R. africae</i> (plus others)	
Rocky mountain spotted fever (North America): <i>Rickettsia rickettsiae</i>	Fever, headache, confusion, and neck stiffness, joint pain, malaise. Macular rash starts at wrists and ankles, spreading to trunk, may be petechial or purpuric. Similar to meningococcal septicaemia. Mortality 30% if untreated
Scrub typhus	
South East Asia: <i>Orientia tsutugamishi</i>	Eschar, painful regional lymphadenopathy, fever, headache, malaise, maculopapular rash in 60%

Q fever

Coxiella burnetii is a disease of rural areas (reservoirs in sheep and cattle) and transmitted by inhalation of infectious particles in dust, contact with infected carcasses (e.g. in abattoirs), and tickbites. There have been recent outbreaks in the Netherlands, Australia, and the Mediterranean and Middle East regions.

- *Presentation:* non-specific symptoms, fever, myalgia, malaise, sweats; dry cough and features of atypical pneumonia; hepatitis; pyrexia of unknown origin (PUO) and splenomegaly.
- *Investigations:* patchy CXR shadowing (lower lobes), hepatic granulomata. Complement fixation tests identify antibodies to phase 1 antigens (chronic infection, e.g. endocarditis; ➡ Infective endocarditis (IE), pp. 102–3) and phase 2 antigens (acute infection). *Treat* with oral doxycycline (to try to prevent chronic infection), co-trimoxazole, rifampicin, or a quinolone.

Human bites

- *Superficial abrasions:* clean the wound. Re-dress the area daily.
- Give tetanus prophylaxis, as needed. Check hepatitis B status, and immunize if necessary (➡ Viral hepatitis, pp. 262–4). HIV counselling and urgent post-exposure prophylaxis (PEP) if indicated (➡ Post-exposure prophylaxis, p. 542–3). HCV has also been transmitted by human bite, so appropriate follow-up needed (there is no HCV PEP).
- Have a low threshold for admission to hospital and IV antibiotic therapy: the human mouth contains a number of aerobic and anaerobic organisms that may produce aggressive necrotizing infection, particularly if the 'closed' spaces of the hand or feet are involved.
- *Antibiotic therapy:* all wounds that penetrate the dermis require antibiotics. Aerobic and anaerobic cultures should be taken prior to treatment with antibiotics. A suggested regimen is co-amoxiclav 500/125mg tds PO or IV. Consult your local microbiologists.
- *Facial bites:* cosmetically significant bites should be referred to a plastic surgeon. Puncture wounds should be cleaned thoroughly and treated with prophylactic antibiotics (as described earlier).
- *Hand bites:* should be referred to the orthopaedic or plastic surgery team; exploration is recommended. Clean the wound thoroughly. Give the first dose of antibiotics IV and subsequent doses PO, unless there are signs of GI upset.

Non-human mammalian bites

- General management is as for human bites (➡ Human bites, p. 495). Clean the wound, swab for aerobic and anaerobic cultures, tetanus prophylaxis as needed, and prophylactic antibiotics (➡ Human bites, p. 495).
- *Rabies* is transmitted by infected saliva inoculated through the skin or by inhalation of aerosolized virus (from infected bats). Presenting features are a viral prodrome, followed by paraesthesiae and fasciculations. Agitation, confusion, muscle spasms, localized paralysis, and brainstem dysfunction follow. There is no effective treatment once symptoms appear; prevention is essential. Rabies prophylaxis (vaccine *plus* rabies-specific Ig) should be considered in all cases if the bite occurred outside the UK, or if the bite was from a bat *within* the UK or from an animal in a quarantine facility. Discuss with local virology or ID experts. For up-to-date advice, see 📖 <https://www.gov.uk/government/publications/human-rabies-public-health-management-of-a-suspected-case>
- *Rabies vaccine* should be given prophylactically (in the deltoid) to those at risk of bites from infected animals (vets, animal handlers, field workers, UK bat handlers), as well as frequent travellers to endemic areas.
- Some Old World monkeys, particularly rhesus and cynomolgus macaques are infected with simian herpes B virus (causes a similar illness in monkeys as HSV does in humans). It can be transmitted by bite and saliva and has caused fatal disseminated infection in humans. If the bite is from a macaque from a colony not deemed clear of the virus, consider starting valaciclovir 1g tds for 14 days, pending further investigation.

Infections in intravenous drug users

Skin and soft tissue infections are common in intravenous drug users (IVDUs) and may be severe, e.g. *Clostridium* spp. and *Bacillus anthracis* infections. DVTs and infected clots may occur. *Staphylococcus aureus* bacteraemia and right-sided endocarditis are serious complications. In the UK, many are HCV-positive, but the minority are HIV- and HBsAg-positive. *S. aureus* bacteraemia and septicaemia are common. Patients with murmurs should have echocardiography to investigate the possibility of endocarditis. Multiple round lung infiltrates ($\pm$ lysis) are characteristic of tricuspid endocarditis with septic emboli.

Cellulitis

- Cellulitis is a relatively common presentation to acute medical services where patients present with a red, hot, swollen, and painful area of skin/soft tissue. This most frequently affects a limb, predominantly a leg. Cellulitis is *almost always unilateral*. Chronic swelling of both legs due to venous insufficiency or cardiac failure is often quite red in appearance. Presentations where both legs are red must be carefully assessed for alternative diagnoses, including dermatitis, vascular phenomena/venous stasis, and haemosiderin deposition.
- Cellulitis is most frequently caused by *S. aureus* or group A *Streptococcus* (or group B, C, or G *Streptococcus* or other organisms less frequently).
- Often there is no clear lesion or ulcer to swab for microbiology, although all patients managed for cellulitis should have an MRSA screen, as confirmed colonization with MRSA would instigate a change in antimicrobial therapy.
- Where IV antimicrobials are indicated, local antimicrobial policies should be observed. Flucloxacillin 2g qds (barring allergy, renal impairment, or drug interactions) is frequently the preferred option. Many patients can be managed with just oral antimicrobials, and a total course length of 10–14 days may be warranted. Clindamycin may be helpful where there is evidence of exotoxin production by the causative organism (blistering, desquamation), although studies on how this alters outcomes are pending.

Necrotizing fasciitis

- Necrotizing fasciitis is a rare infection of the subcutaneous tissues that tracks along fascial planes. It is usually caused by group A streptococci but may also be polymicrobial. Urgent surgical debridement is the mainstay of treatment. Samples should be sent for urgent Gram stain, as well as culture and sensitivity testing.
- Patients are usually extremely unwell. Consider this diagnosis in all patients with skin/soft tissue infection who appear disproportionately septic or where there is disproportionate pain.
- Erythematous, exquisitely tender area, sometimes with underlying crepitus. X-ray may show gas in subcutaneous tissues.
- Mainstay of treatment is *urgent* debridement of all necrotic tissue by senior surgeon. Further imaging prior to theatre merely delays the procedure without providing further therapeutic information.
- Clindamycin is an important component of any antimicrobial therapy, which inhibits bacterial exotoxin production. Advice should be sought from local microbiology/ID experts, but one suggested treatment regime is ciprofloxacin 400mg bd IV, clindamycin 600mg–1.2g qds IV, benzylpenicillin 1.2–2.4g 4-hourly. For necrotizing fasciitis infections in IVDUs, complex regimes may be needed—take advice from microbiology or ID specialists.
- Patients usually require daily debridement in theatre, followed by reconstructive surgery.

Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)

- SARS and MERS are severe respiratory illnesses caused by coronaviridae. SARS was first reported in China in 2002 and spread worldwide before waning in 2004. Re-emergence of SARS remains a possibility, and other coronaviruses, such as Middle East respiratory syndrome coronavirus (MERS-CoV), is an ongoing problem.
- These coronavirus infections have a high transmission rate to close respiratory contacts, particularly health-care workers. Also probable transmission by fomites. Risk assessment guidance for patients suspected of having these respiratory viruses can be found at  <https://www.gov.uk/government/publications/mers-cov-risk-assessment>
- Causes fever, myalgia, and variable pneumonic illness, with possible rapid deterioration. High mortality in patients >60 years.
- Strict isolation and rigorous enforcement of infection control essential.
- Treatment as yet undefined. High-dose steroids may be of some benefit in severely ill. Ribavirin is probably of no value.

Bioterrorism

- Possible agents of bioterrorism include anthrax (*B. anthracis*), botulism (*Clostridium botulinum*), brucellosis (*Brucella melitensis* associated with goats and *Brucella abortus* from other livestock), glanders/melioidosis (*Burkholderia mallei*, *Burkholderia pseudomallei*), plague (*Yersinia pestis*), Q fever (*C. burnetti*), smallpox, tularaemia (*Francisella tularensis*), and VHFs.
- There is increasing awareness of the possibility of a deliberate release of biological and chemical agents. Historically, plague, *Salmonella* spp., and anthrax have all been used, as have nerve gases and biological toxins. More recent large-scale releases have been Sarin gas (a nerve gas) on the Tokyo underground in 1995 and anthrax spores (as a white powder in the mail) in the USA in 2001.
- Releases are likely to be either airborne or food and water contamination.
- Clues that a deliberate release may have occurred would be the unexpected appearance of an infection outside its normal range (e.g. anthrax in a city), an infection appearing in a patient unlikely to contract the disease, or a sudden cluster of patients with the same pattern of symptoms. 'White powder' incidents also continue to cause concern.
- Any suspicion of a deliberate release should be communicated urgently to the consultant microbiologist and Public Health practitioner (CCDC) on-call.

(See Table 7.5.)

Table 7.5 Characteristics of some bioterrorism agents

Agent	Clinical	Person-to-person transmission risk	Treatment	Prophylaxis
Smallpox	Initially macules, then deep vesicles predominantly on peripheries (of chickenpox superficial vesicles predominantly on trunk)	Yes	Supportive	Vaccination (post-exposure vaccination effective)
Plague	Likely to be pneumonic, with severe sepsis in inhalational plague	Yes	Gentamicin, streptomycin, ciprofloxacin	Ciprofloxacin, doxycycline
Tularaemia	Likely to be flu-like or pneumonic, with sepsis in inhalational tularaemia	Very low possibility, but respiratory precautions advisable	Gentamicin, ciprofloxacin	Ciprofloxacin, doxycycline
Anthrax— inhalational	Sepsis, haemorrhagic mediastinitis (widened mediastinum), may be minimal pneumonitis	Highly unlikely	Ciprofloxacin, doxycycline	Ciprofloxacin, doxycycline, vaccination
Anthrax— cutaneous	Necrotic ulcer with marked surrounding oedema	Highly unlikely	Ciprofloxacin, doxycycline	Ciprofloxacin, doxycycline, vaccination
Anthrax—white powder incident	Necrotic ulcer with marked surrounding oedema	Highly unlikely If powder contains anthrax spores, then highly infectious. Controlled decontamination essential	Ciprofloxacin, doxycycline	Ciprofloxacin, doxycycline, vaccination

Melioidosis	Likely to present as septicaemic illness, but spectrum of illness	Ceftazidime, meropenem
Botulism	Multiple cranial nerve palsies, other palsies. No alteration in conscious level	Antitoxin given on clinical suspicion?
VHFs	Haemorrhagic illness with fever	Ribavirin for Lassa and CCHF Ribavirin for Lassa and ? CCHF
Nerve gases	Anticholinesterase inhibitors, salivation, bronchorrhoea, sweating, bronchospasm, bradycardia, abdominal cramps, diarrhoea, miosis, muscle fasciculation, weakness, respiratory paralysis, tachycardia, hypertension, emotional lability, confusion, ataxia, convulsions, coma, central respiratory depression	Supportive, atropine, pralidoxime, diazepam

Tuberculosis

Mycobacterium tuberculosis is a widely disseminated bacteria, estimated to have colonized up to a third of the world's population. The risk of developing clinical disease is 5% in the first 5 years after exposure, and an additional 5% over subsequent lifetime. In the UK, the incidence of TB is increasing, and changing patterns in presentation can make acute clinical assessment complex.

Presentation

- Confirm any risk factors for TB, including: immigration from an area of high incidence, homelessness, alcohol misuse, DM, immunosuppression (including from HIV, or iatrogenic).
- Pulmonary: worldwide 90% of cases, in the UK only 50%; typically indolent presentation; productive cough, fever, sweats, weight loss. While these symptoms should prompt a search for TB, lymphoma and some other conditions can also present like this.
- Extra-pulmonary: pleural TB can present similarly to pulmonary disease; nodal disease often just with fever, sweats, and weight loss; GI and genitourinary disease can also present with indolent non-specific symptoms, or with abdominal or flank pain; skeletal TB most frequently affects the spine but may also present with monoarthritis (most frequently the knee, but other joints may be affected); CNS TB can present with headaches, confusion, or reduced GCS scores. Less commonly, erythema nodosum, pericardial disease, or scrofuloderma may be apparent.
- In the immunocompromised or elderly, classic symptoms may be absent.

Investigations

- **Radiology:** CXR changes in pulmonary disease typically include apical consolidation, often with paratracheal adenopathy. In extra-pulmonary disease, CT can be suggestive, but there are few pathognomic signs.
- **Microbiology:** in pulmonary disease, sputum ($\times 3$) for ZN/auramine stain can give an indication of disease within 24h, but sensitivity is typically ~30–40%; culture usually becomes positive at 10–14 days but can take up to 6 weeks. In those not expectorating, BAL or an enterostripping may be used, and in children, gastric aspirates are useful. In extra-pulmonary disease, obtaining tissue for culture is key. In CNS disease, the CSF typically demonstrates 10–1000 WCC/microlitre, a low glucose, and a high protein, but it is rarely ZN-positive. Culture may take up to 6 weeks and antimicrobial susceptibility testing typically takes a further 2 weeks.
- **Nucleic acid tests:** PCR for TB is advocated for respiratory samples and has a higher sensitivity than ZN staining. It can also be used to discern rifampicin resistance and is recommended by NICE when risk factors for multidrug-resistant (MDR)-TB are present. PCR on samples other than sputum has a lower sensitivity.
- **Interferon-gamma release assay:** the enzyme-linked immunospot (ELISpot) or QuantiFERON® tests indicate previous exposure to *M. tuberculosis* (i.e. are tests for latent disease) but do not give an indication of active disease and can actually give a false negative result in some instances of active disease and in some immune-deficient states.

Management

- *Refer*: involve ID/respiratory teams early when TB is in the differential; alert the microbiology laboratory as to clinical suspicion, so samples can be appropriately processed.
- *Drug treatment*: focuses on combination therapy. This should only be initiated by, or on the advice of, a clinician experienced in treating TB. In acute medicine, the only urgent indication to start TB therapy is CNS disease. The standard regime is quadruple therapy for 2 months (see Box 7.7), then dual therapy for a further 4 months in pulmonary disease, extending to complete 9–12 months in total for some extra-pulmonary disease.
- *Drug resistance*: currently isoniazid mono-resistance is ~10% in the UK, with MDR at ~1–2% and very few cases of extended drug resistance.
- *Steroids*: only definitively indicated in CNS and pericardial disease.

Public Health

- *Isolation*: a side room with respiratory precautions for suspected pulmonary disease. Negative pressure ventilation is indicated for drug-resistant cases.
- *Notification*: TB is notifiable, and the local Health Protection Team should be made aware by the treating physician upon making or suspecting the diagnosis.
- *Limiting transmission*: compulsory treatment for patients with pulmonary TB who decline therapy is not possible; for patients at risk of non-compliance, involving a TB expert early is crucial.

Box 7.7 First-line pharmacotherapy for tuberculosis

This should only be instigated on the advice of a physician experienced in the management of TB. Risk-assess for MDR-TB and for the risk of HIV before commencing.

- Induction (2 months):
 - Rifampicin 450mg (<50kg) or 600mg (>50kg) PO od.
 - Isoniazid 300mg PO od.
 - Ethambutol 15mg/kg PO od.
 - Pyrazinamide 1.5g (<50kg) or 2g (>50kg) PO od.
- Maintenance (4 months for pulmonary; 7–10 months for non-pulmonary disease):
 - Rifampicin 450mg (<50kg) or 600mg (>50kg) PO od.
 - Isoniazid 300mg PO od.
- Steroids (on discussion with a specialist and only indicated in TB meningitis and pericardial TB):
 - TB meningitis: dexamethasone 0.4mg/kg/day (if coma or focal signs) or 0.3mg/kg/day (if no coma/focal signs), usually given in four divided doses, and very slowly withdrawn over the following 8 weeks.
 - Pericardial TB: a glucocorticoid equivalent to prednisolone at 60mg/day.

Emergencies in HIV-positive patients

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Emergency presentations of HIV infection

Patients with HIV infection may present with:

- HIV-related or HIV-unrelated problems.
- Toxicity related to anti-HIV therapy.
- Primary HIV infection (PHI) (seroconversion).

It is important to recognize and diagnose HIV infection in individuals in whom this has been previously unrecognized, and identify patients who may have been exposed to HIV and who may need treatment.

Where there is local expertise in the management of HIV infection, it is recommended that care is provided in consultation with the appropriate team. It is essential to consult with specialists before prescribing any specific treatments.

General principles

- The use of combination antiretroviral therapy is very successful. HIV is now considered to be a chronic manageable disease. Successful antiretroviral therapy significantly increases the CD4 count and reduces the risk of opportunistic complications. Highly active antiretroviral therapy (HAART) reduces HIV RNA load to undetectable levels (e.g. <20 copies/mL of plasma) in >95% of patients.
- Patients with known or suspected HIV infection should be investigated and managed aggressively.
- Unusual opportunistic infections and malignancies are more common and may occur simultaneously or sequentially.
- Toxicity from antiretroviral therapy may present to acute medical services.
- Drug interactions with antiretroviral therapy are common.
- Common diseases still affect HIV-positive individuals but may present atypically.
- All patients should have a full examination, including a careful examination for unusual rashes, skin lesions, and lymphadenopathy, as well as the mouth. Examination of the mouth can reveal a great deal of information regarding the level of immunity [e.g. oral thrush and hairy leukoplakia suggest ↓ immunity and risk of severe opportunistic infections; Kaposi's sarcoma (KS) suggests ↑ risk of visceral KS].
- *Indicator diseases* that should alert the clinician to investigate for HIV include TB, candidiasis, cryptococcosis, cryptosporidiosis, CMV infections, KS, and toxoplasmosis (see Table 8.1).
- Always consider the possibility of HIV in patients from sub-Saharan Africa and men who have sex with men (MSM).
- The acute physician may be the first to consider HIV in previously undiagnosed patients.

(See Box 8.1.)

Box 8.1 Key points: acute presentations of HIV-positive patients

- Common diseases still affect HIV patients but may present atypically.
- Think of unusual opportunistic infections and malignancies.
- Always consider toxicity from antiretroviral therapy.
- Many drugs interact with antiretroviral therapy.

HIV testing

In most situations, HIV testing is carried out with informed consent by genitourinary medicine (GUM)/sexually transmitted infection (STI) clinics, in primary care, or as part of routine antenatal care. However, the presentation of individuals with potentially HIV-related complications or at potential risk of previous HIV exposure to the emergency clinician provides an opportunity to diagnose the infection. While most choose to have an HIV test within the confidential setting of a specific HIV-testing service, any health-care provider should possess the essential skills for appropriate discussion of HIV testing. HIV testing should no longer be exceptional but should be considered with informed consent in all patients with clinical indicator diseases or presentations.

Pretest discussion

In-depth discussion is only necessary where there is a high probability of a positive result, otherwise a simple yes/no question may be appropriate. If the patient declines or has further questions, then it is important to dispel any misconceptions and detail the benefits of testing (specifically that early diagnosis has a better prognosis through access to treatment and that the disease, while currently incurable, has a good life expectancy, etc.). If the chance of a positive result is high, more detail about testing should be given prior to testing. The following issues should be included in a 'pretest' discussion:

- Rationale for testing (see Box 8.2).
- Benefits of knowing the status.
- When and by whom the result will be given.
- 'Window period' of infection (i.e. may take up to 8 weeks from exposure for an HIV antibody test to become positive).
- Confidentiality: testing for HIV, and any result whether positive or negative, does not require disclosure to a GP. A positive result does not necessarily need to be disclosed to third parties without consent but will have implications for insurance/mortgages.

Post-test discussion

The following principles should be followed in a 'post-test' discussion:

- Giving a positive result should follow the principles of breaking bad news.
- If a result is positive, early referral to an HIV clinician is essential.
- If a result is negative, the window period should be reinforced (particularly in situations where seroconversion is suspected;  Primary HIV infection, p. 510).
- If a result is negative, the opportunity for future risk reduction should be considered.

HIV testing without consent

It is rarely necessary to test for HIV infection without consent. However, this is justified in the following settings:

- Testing of organ transplantation donors.
- Testing of the unconscious/confused patient where HIV infection is suspected and the management of the patient will be materially changed by knowledge of their HIV status.

- Testing of the unconscious patient who is the 'donor' in a significant needle-stick/splash injury. In this situation, testing is justified if the patient is unlikely to regain consciousness for 48h but should only be performed on a blood specimen that has been previously taken for another purpose.
- Given the potential litigation arising from HIV testing without consent, it is advisable to seek a second opinion (preferably from a physician with HIV experience) that such testing is justified.

Universal HIV testing is recommended in the following settings

- GUM or sexual health clinics.
- Antenatal services.
- Termination of pregnancy services.
- Drug dependency programmes.
- Health-care services for those diagnosed with TB, viral hepatitis B or C, and lymphoma.
- In areas of >2/1000 prevalence, routine screening for all new registrations with a GP and all medical admissions to hospital.

HIV testing should be routinely recommended to the following

- All patients presenting for health care where HIV or HIV indicator diseases enter the differential diagnosis (see Table 8.1; ➡ Primary HIV infection, p. 510).
- All patients diagnosed with an STI.
- All sexual partners of men and women known to be HIV-positive.
- All men who have disclosed sexual contact with other men.
- All ♀ sexual contacts of MSM.
- All patients reporting a history of injecting drug use.

All men and women from a country of high HIV prevalence.

- All men and women who report sexual contact abroad or in the UK with individuals from countries of high HIV prevalence.

Box 8.2 Rationale for HIV testing

- A quarter of people with HIV are diagnosed late.
- Prognosis is much poorer with late diagnosis; early diagnosis improves prognosis.
- Twenty per cent of people living with HIV are undiagnosed but are thought to account for up to 50% of onward transmission.
- Knowledge of HIV-positive status has been associated with reduced transmission rates; therefore, testing and diagnosis should reduce the incidence of HIV infection.

Further information can be found at: 🌐 <https://www.bhiva.org/HIV-testing-guidelines>

Primary HIV infection

PHI (also known as HIV seroconversion illness) is easily overlooked. Intervention may help prevent further spread of HIV (individuals recently infected with HIV are thought to be highly infectious, particularly if unaware of their status).

Risk of recent infection

A significant history of exposure to a potential HIV source within the last 3 months (sexual, percutaneous, or mucocutaneous), in conjunction with any of the features listed here, warrants performing specific diagnostic tests for PHI.

Symptoms and signs

- Typically within 2–4 weeks of exposure but can be up to 3 months.
- Flu-like illness (fever, myalgia, headache, lymphadenopathy, retro-orbital pain).
- Maculopapular rash (differential diagnosis of secondary syphilis).
- Pharyngitis/oral ulceration.
- Concomitant STIs (e.g. primary or secondary syphilis, gonorrhoea, genital ulcer disease).

Laboratory findings

- HIV antibody tests may be negative at the time of seroconversion, and an HIV RNA viral load test may be required to confirm the diagnosis.
- Lymphopenia, thrombocytopenia, and raised ALT/AST may occur.

Sequelae of acute immunosuppression

- CD4 count may transiently fall to <200 cells/mm³ (therefore, risk of opportunistic infections, particularly PCP).
- Candidiasis, viral warts, VZV.

Management

- The diagnosis of PHI will enable appropriate partner notification, screening for other STIs, and strategies to reduce onward transmission.
- The decision of when to start HIV therapy is complex and should only be undertaken by clinicians experienced in this. There is growing evidence that early treatment improves outcomes and reduces population reservoirs, reducing transmission.
- New infections may have resistance to one or more antiretroviral agents—knowledge of local resistance rates and the patient's resistance profile is desirable before initiating antiretroviral therapy.
- Early referral to an HIV specialist is essential. Patients should be seen by an HIV specialist within 24h if symptomatic/hospitalized with HIV or within 2 weeks otherwise.

Presentation with HIV complications and opportunistic infections

Degree of immunosuppression

- The normal CD4 count is $500\text{--}1500 \times 10^6$ cells/mm³ and gradually decreases during the course of HIV infection.
- The CD4 count is used as a guide to a patient's susceptibility to complications of HIV infection (see Fig. 8.1). For example, *Pneumocystis jiroveci* (formerly known as *P. carinii*) pneumonia (PCP) is uncommon with a CD4 count >200.

Patients (who are aware of their HIV status) are usually familiar with these measures and are likely to be aware of their most recent results.

Risk group and predisposition to different complications

HIV in the UK is predominantly seen in specific patient groups, and the incidence of HIV-related complications varies between these groups.

- MSM have a higher incidence of KS than other Caucasians.
- Injecting drug users are more likely to be co-infected with hepatitis C and to develop sepsis related to injecting.
- Individuals of African or Asian origin are more likely to present with TB (which may be atypical and/or extra-pulmonary in presentation).
- Individuals of African origin are more likely to experience cryptococcal infection.

Travel history

Many infections in the HIV-infected patient represent reactivation of latent pathogens, and a travel history is helpful in the differential diagnosis, particularly for individuals presenting with pyrexia.

- Histoplasmosis: travel to central America and eastern USA.
- Coccidiomycosis: travel to South West USA and parts of South America.
- Penicilliosis: travel to countries in South East Asia and Indonesia.
- *Strongyloides* hyperinfection: previous travel in the tropics.
- Leishmaniasis: travel in the Mediterranean, the Middle East, and the tropics.

Antiretroviral therapy

- Patients who respond well to antiretroviral therapy (i.e. low HIV RNA load with a significant increase in CD4 count) have a markedly reduced risk from opportunistic complications of HIV infection. General medical/surgical conditions should be considered as being equally likely in successfully treated patients, as well as in those with untreated HIV infection with a high CD4 count.
- However, antiretroviral therapy can cause toxicity and may present to the emergency clinician (☹ Antiretroviral toxicity, pp. 538–9).
- Caution should be exercised when prescribing other drugs; use this from the University of Liverpool: ☞ <https://www.hiv-druginteractions.org/>

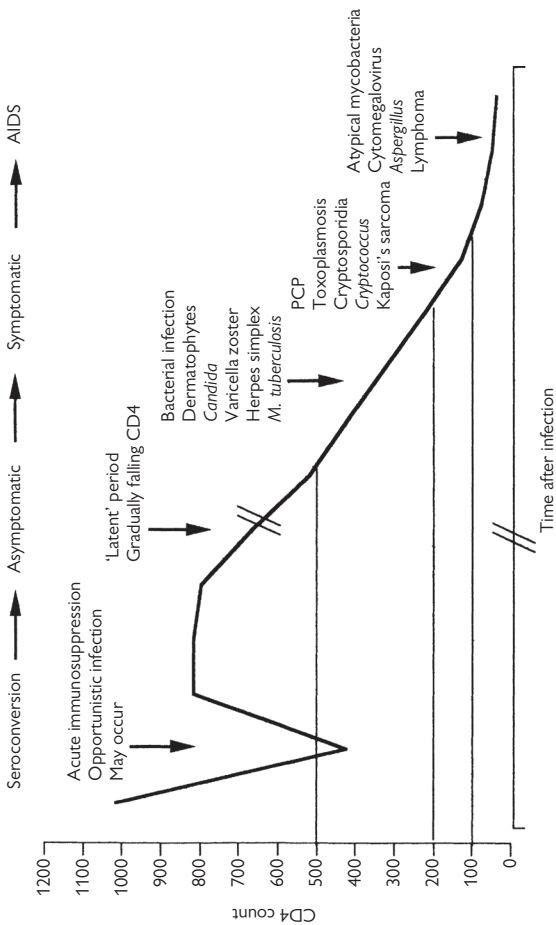


Fig. 8.1 CD4 count is used as a guide to a patient's susceptibility to complications of HIV infection.

Clinical indicator diseases for adult HIV infection

(See Table 8.1.)

Table 8.1 Clinical indicator diseases for adult HIV infection	
AIDS-defining conditions	Other conditions where HIV testing should be considered
<i>Respiratory</i> • TB • PCP	Bacterial pneumonia Aspergillosis
<i>Neurology</i> • Cerebral toxoplasma • Primary cerebral lymphoma • Cryptococcal meningitis • Progressive multifocal leukoencephalopathy (PML)	Aseptic meningitis/encephalitis Cerebral abscess Space lesion of unknown cause GBS Transverse myelitis Dementia Peripheral neuropathy
<i>Dermatology</i> • KS	Severe psoriasis Severe seborrhoeic dermatitis Multi-dermal zoster
<i>Gastroenterology</i> • Persistent cryptosporidiosis	Oral candidiasis Oral hairy leukoplakia Chronic diarrhoea (unknown cause) Weight loss (unknown cause) HBV or HCV infection <i>Salmonella, Shigella, or Campylobacter</i>
<i>Oncology</i> • Non-Hodgkin's lymphoma	Hodgkin's lymphoma or Castleman's Anal cancer or dysplasia Lung cancer Seminoma Head and neck cancer
<i>Gynaecological</i> • Cervical cancer	Cervical or vaginal dysplasia
<i>Haematological</i>	Any unexplained blood dyscrasia
<i>Ophthalmological</i> • CMV retinitis (see Fig. 8.2)	Any infective retinitis (zoster, <i>Toxoplasma</i>)
<i>ENT</i>	Lymphadenopathy (unknown cause)
<i>Other</i>	PUO or STI, mononucleosis-like syndrome

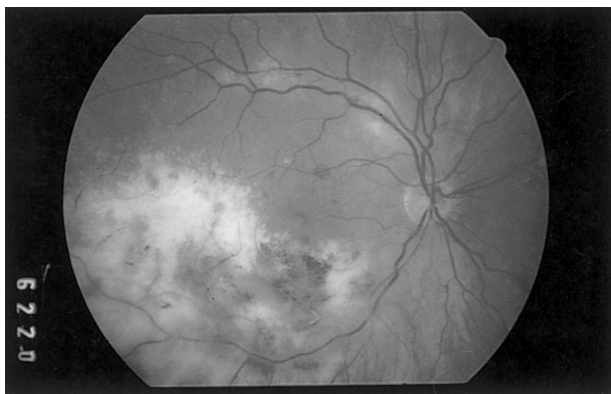


Fig. 8.2 The typical appearance of CMV retinitis in a patient with AIDS, characterized by retinal necrosis with an irregular granular border, patchy retinal haemorrhage, and retinal inflammatory sheathing of the retinal vessels.

Reproduced from Easty D, et al. *Oxford Textbook of Ophthalmology*, 1999, with permission from Oxford University Press.

Acute neurological conditions in HIV-positive patients: assessment

Opportunistic infections and malignancies, the direct effect of HIV itself, and antiretroviral drugs can all cause disease of the CNS or peripheral nervous system. The presenting features of different conditions are often varied and non-specific and tend to involve the same diagnostic approach and investigations.

Key symptoms and signs

- *General*: look for evidence of advanced immunosuppression (see Fig. 8.1).
- *Unconsciousness*: assess and manage as described under  **Coma**: assessment, pp. 348–9.
- *Seizure*: requires urgent contrast CT, or preferably MRI, head scan to detect an SOL and, if none detected, suitability for diagnostic LP. Consider anti-epileptics, but be aware of antiretroviral and other drug interactions (sodium valproate commonly recommended if receiving protease inhibitor or non-nucleoside therapy). Lorazepam is preferable to diazepam for terminating seizures.
- *Headache*: elucidate symptoms of raised ICP suggestive of an SOL such as nausea, early morning headache, and intensity on coughing. Distinguish from facial pain caused by dental, sinus, or herpetic neuralgia (check for herpetic rash).
- *Meningism*: may be reduced or absent due to reduced inflammatory response. Aseptic meningitis can occur during PHI (seroconversion illness). With advancing immunosuppression, viral, bacterial, tuberculous, and fungal (cryptococcal) meningitides are more common and may not manifest typical signs of meningism.
- *Paraparesis*: consider viral transverse myelitis (HIV, CMV, VZV, or HSV) or cord compression by infection or malignancy. Requires urgent MRI spine and subsequent LP if not contraindicated.
- *Cognitive impairment*: wide differential. If associated with any focal neurological signs, consider SOL, PML, HIV dementia, and late syphilis.
- *Psychiatric disturbances*: an organic cause is often found. May be a result of antiretroviral drugs themselves or their interactions with antipsychotic and recreational drugs. If aggressive, ensure the patient has no access to contaminated sharps.
- *Peripheral neuropathy*: typically of gradual onset and caused by certain antiretrovirals or HIV itself.
- *Myopathy*: zidovudine (AZT) and integrase inhibitors can cause myopathy or even rhabdomyolysis (check CK and renal function), arising from mitochondrial toxicity ( Antiretroviral toxicity, pp. 538–9). It may also be due to the concomitant use of lipid-lowering agents, and some antiretrovirals increase the levels of statins.
- *Rapid visual deterioration*: consider CMV-related retinitis (often apparent on fundoscopy), *Toxoplasma* uveitis, endophthalmitis, intracerebral causes, and syphilis. Retinal detachment may be a consequence of treatment. Immediate referral to an ophthalmologist.

Acute neurological conditions in HIV-positive patients: investigations

Blood tests

- **Baseline** (useful if already done—the patient will often know the results): CD4 cell count (but beware of CD4 counts taken during acute infections—these can be misleading), HIV RNA viral load, serology for *Toxoplasma* IgG (positive in >90% of patients with cerebral toxoplasmosis, indicative of risk of reactivation), CMV IgG, serological tests for syphilis (STS).
- **Routine**: FBC (low lymphocyte count may give a clue to CD4 depletion), U&Es, LFTs.
- **Acute**: inflammatory markers (CRP and ESR), syphilis testing, LDH (may be raised in lymphoma), blood cultures [bacterial, mycobacterial (4–6 weeks)]. Measure peripheral blood CMV DNA by PCR and serum cryptococcal antigen (CrAg) if CD4 count <200 cells/mm³ (positive in >80% with cryptococcal meningitis).

Specific

- **Stool, urine, and throat cultures**: see Box 8.3 for LP.
- **CXR**: consider TB at any CD4 count. Para-aortic and hilar lymphadenopathy might suggest *Mycobacterium avian intracellulare* (MAI) or lymphoma.
- **Contrast CT or MRI scan of the head**:
 - Contrast essential, MRI more sensitive than CT (risk of missing brainstem disease, *Toxoplasma* cysts, and PML by CT).
 - Contrast-enhancing SOL very likely to be either cerebral toxoplasmosis (typically multiple, with ring enhancement, associated with oedema, at the basal ganglia or grey–white matter interface) or cerebral lymphoma (typically fewer lesions, with irregular enhancement, associated with oedema, periventricular). Poor response to empirical toxoplasmosis treatment suggests lymphoma. Less commonly, consider bacterial (e.g. *Streptococcus*, *Nocardia*), mycobacterial (e.g. tuberculoma), or fungal (e.g. cryptococcoma) lesions. Mycobacterial disease is on the increase, especially in ‘high-risk’ populations, e.g. patients from endemic TB areas.
 - Meningeal enhancement and hydrocephalus can occur in tuberculous, cryptococcal, or syphilitic meningitis.
 - PML: non-enhancing, multifocal, subcortical white matter changes. No mass effect.
 - HIV-associated dementia: non-enhancing, diffuse, deep white matter hyperintensities, with prominent cerebral atrophy. No mass effect.
 - Viral encephalitis (typically CMV, HSV, VZV) may display variably enhancing confluent changes, but often normal.

- *Brain biopsy*: if disease stage and general prognosis fair, consider performing if no response to empirical treatment.
- *EEG*: is useful to confirm seizure activity and response to treatment, but often non-specific for HIV encephalopathy and opportunistic infections.
- *Contrast MRI of the spine*: the best modality for spinal cord and nerve root imaging.
- *NCS/EMG*: useful if unusual or treatment-unresponsive sensory or motor symptoms and signs.

Box 8.3 Lumbar puncture

- Arrange for contrast CT or MRI head before any LP, and ensure that there are no clotting abnormalities.
- Always measure the opening pressure (high in cryptococcosis).
- Collect 6–8mL of CSF, and divide into four universal containers and one fluoride tube for glucose (always take paired blood for glucose and protein).
- Bottles 1 and 4 to microbiology for:
 - RBC and WBC estimation.
 - Bacterial: MC&S.
 - Mycobacterial: ZN microscopy, culture, and consider PCR.
 - Viral: PCR for CMV, HSV, VZV, JC virus (PML), EBV (lymphoma).
 - Other: Indian ink microscopy and CrAg (near 100% sensitivity and specificity for neurological cryptococcal disease), fungal culture, and STS.
- Bottle 2 and both fluoride tubes to biochemistry for protein and paired glucose measurement.
- Bottle 3 to cytology (rarely diagnostic) or immunology, if indicated.
- Raised CSF cell count and protein (up to 1g/L) can be an incidental finding in asymptomatic HIV infection; conversely, there may be little inflammatory response, e.g. in cryptococcal meningitis.

Acute neurological conditions in HIV-infected patients: treatment

(See Table 8.2.)

Condition	Possible presentations	Diagnostic tests	Treatment
HIV	Encephalitis or aseptic meningitis Dementia/psychiatric presentation Seizures	Diagnosis of exclusion Brain biopsy diagnostic, but not performed for this reason	HAART
Toxoplasmosis	SOL Seizures Confusion Encephalitic illness	90% anti- <i>Toxoplasma</i> antibody positive but does not discriminate active from inactive disease CT: ring-enhancing lesions Brain biopsy gold standard, perform if no response to empirical therapy	Sulfadiazine 1–2g IV/PO qds + pyrimethamine 100mg PO od on first day, then 75mg PO od + folic acid 15mg PO od for 4–6 weeks Clindamycin 1.2g PO/IV qds + pyrimethamine 100mg PO od on first day, then 75mg PO od + folic acid 15mg PO od Atovaquone 750mg PO tds for 21 days (consider use of dexamethasone to reduce cerebral oedema)
Cryptococcosis	Headache± meningism SOL (cryptococcoma) Seizures Confusion	CSF: pleiocytosis with low glucose but may be normal in 20–30%. India ink stain, culture, and CrAg Serum CrAg positive in 95%	Amphotericin 0.25mg–1mg/kg IV od for up to 6 weeks ± flucytosine 100mg/kg PO/IV qds for 2 weeks (liposomal formulations may be used if concerns regarding nephrotoxicity) Fluconazole 400mg bd, daily/regular LPs to reduce ICP ≤20cmH ₂ O is essential
Mycobacterium	Headache ± meningism	CSF: pleiocytosis with low glucose in most cases; ZN stain positive in only 10–20%. CSF culture takes 4–6 weeks	Obtain specialist microbiological advice; initiate therapy with at least four agents (preferably including those with CNS penetration, i.e. isoniazid + pyrazinamide), and consider steroids if fits or worsening neurological signs

<i>Nocardia</i>	Headache ± meningism, SOL (tuberculoma) Seizures Confusion	Brain biopsy/culture Often coexisting pulmonary disease	Combination of at least 2 of co-trimoxazole, amikacin, streptomycin, imipenem (or meropenem) and minocycline
CMV	Encephalitis Transverse myelitis Polyradiculitis	Viral detection in CSF or neural tissue. PCR, culture, or immunohistochemistry	Ganciclovir 5mg/kg IV bd for 3 weeks Valganciclovir 900mg PO bd for 3 weeks Foscarnet 90mg/kg bd IV for 3 weeks
Varicella-zoster	Encephalitis Transverse myelitis Polyradiculitis	Viral detection in CSF or neural tissue. Culture, immunohistochemistry, or PCR	Aciclovir 10mg/kg IV tds for 10 days Aciclovir 800mg five times daily for 5–10 days Valaciclovir 1g PO tds for 1 week
Herpes simplex	Encephalitis Radiculitis Seizures	Viral detection in CSF or neural tissue. Culture, immunohistochemistry, or PCR	Aciclovir 10mg/kg IV tds for 14–21 days
PML (JC virus)	Motor dysfunction Cranial nerve palsies Dementia	CSF: anti-JC virus antibodies Brain biopsy White matter MRI/CT changes	HAART
Lymphoma	SOL Malignant meningitis Isolated nerve or spinal cord lesion	CSF cytology Brain biopsy	HAART + chemotherapy (treatment or palliative) + intracranial irradiation

Check BNF for contraindications, cautions, side effects, and interactions.

Respiratory emergencies in HIV-positive patients: assessment

Caution: HIV-infected patients presenting with cough warrant a high index of suspicion for *M. tuberculosis* which may be MDR. Such patients should wear a filter mask and be admitted to a side room. If on a ward with other immunocompromised patients, this should be with negative-pressure isolation facilities.

Key symptoms and signs

- **General:** examination, including the oropharynx and lymphatic system, can give useful clues. Look for evidence of advanced immunosuppression and extra-pulmonary clues to the aetiology (e.g. cutaneous KS, neurological signs due to cryptococcosis, or retinitis due to CMV). Remember—multiple pathologies can coexist.
- **Cough productive of sputum:** purulent sputum suggestive of bacterial or mycobacterial aetiology (incidence of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and TB up to 100-fold higher than in HIV-negative controls). Also consider *Staphylococcus aureus* (in IVDUs) and Gram -ve organisms (e.g. *Pseudomonas aeruginosa*).
- **Non-productive cough:** in patients with CD4 cell count <200 cells/mm³, the main concern is *Pneumocystis jiroveci* (previously *carinii*, a fungus) pneumonia (PCP), which typically has a chronic, progressive history associated with breathlessness (see Table 8.3). PCP can occasionally occur in patients during PHI (seroconversion illness) and can be seen in patients despite good adherence to co-trimoxazole prophylaxis. Other causes of non-productive cough include viral URTIs (any CD4 count), KS, lymphoma, and rarely lymphocytic interstitial pneumonitis (any CD4 count, but typically raised CD8 cell count with Sjögren's symptoms).
- **Haemoptysis:** is suggestive of mycobacterial or fungal causes, PE, or KS.
- **Breathlessness:** if sudden onset, consider pneumothorax (secondary to PCP), pulmonary oedema, or PE. If gradual and progressive, need to exclude PCP.
- **Chest pain:** is more common in bacterial infections, KS, pneumothorax, and PE. HIV-infected patients are more at risk of thromboembolic disease. Pneumothorax may complicate up to 10% of patients with PCP.

Table 8.3 Clinical, laboratory, and CXR findings that may distinguish PCP from bacterial pneumonia

Findings	PCP	Bacterial
CD4 cell count	<200 cells/mm ³	Any
Symptoms	Non-productive cough	Productive cough Purulent sputum
Symptom duration	A few weeks	3–5 days
Signs	Occasionally bilateral fine crackles (usually minimal signs)	Focal lung signs
Laboratory tests	WBC variable	WBC frequently elevated
Chest radiograph findings		
Distribution	Diffuse > focal	Focal >diffuse
Location	Bilateral, perihilar initially	Unilateral, segmental/lobar
Pattern	Diffuse, interstitial infiltrates	Often lobar or focal consolidation
Cysts	10–15%	5–10% (<i>Klebsiella</i> , staphylococcal)
Pleural effusions	Very rare	25–30%

Practice points

- Beware 'normal' CXR: respiratory history is the most important.
- If CD4 count <200 cells/mm³ and the history is compatible, consider PCP as the most likely respiratory infection, and start empirical therapy.
- Diagnostic investigations should be done as soon as possible.
- TB is still common among people living with HIV in the UK.

Respiratory emergencies in HIV-positive patients: investigations

Non-invasive investigations

NB Viral and fungal infections may cause few symptoms and signs—if suspected, request viral PCR and fungal microscopy and culture, in addition to the investigations listed here:

- *Baseline (useful if already done)*: CD4 cell count, HIV RNA viral load.
- *Radiology*: CXR (see Table 8.4). Other radiology, such as US, CT, or HRCT, performed as needed.
- *FBC*: leucopenia suggests poor prognosis in bacterial infections, and if pre-existing, can guide choice of empirical therapy.
- *U&Es*: low Na^+ or renal impairment suggests poor prognosis.
- *LFTs*: abnormalities suggest disseminated disease or other pathology.
- *Serology*: for *Legionella* (frequently tested by detection of urinary antigen), *Mycoplasma*, and other atypical pathogens.
- *Serum CrAg*: a test with >90% sensitivity and >95% specificity for systemic cryptococcaemia.
- *ABGs*: hypoxia can occur in any pneumonic process, but most characteristic of PCP.
- *Mantoux test (tuberculin skin testing)*: results can be misleading or unhelpful, as anergy is common. Only used in specific circumstances.
- *Exercise O_2 saturation*: significant exercise desaturation very suggestive of a diffuse pneumonitis such as PCP. Useful in patients with ‘normal’ CXR and SaO_2 >93% at rest.
- *Lung function tests*: if available, these may be useful as impaired gas transfer (KCO) has the same significance as O_2 desaturation.
- *Blood cultures*: often positive in *S. pneumoniae* infections. Mycobacterial blood cultures may be useful (4–6 weeks).
- *Sputum cultures*: for microscopy and culture (including mycobacteria).
- *Induced sputum*: nebulized hypertonic saline administered by specialist nurse or physiotherapist. Silver stain or immunofluorescence of induced sputum or BAL fluid has a sensitivity of 90% for PCP. Also send samples for microscopy and culture (bacterial and mycobacterial). Do not perform on an open ward.

Invasive investigations

- *Bronchoscopy*: usually indicated if no response to treatment or second pathology suspected. Look carefully for KS lesions (transbronchial biopsies not routinely taken as risk of pneumothorax and haemorrhage). Send BAL samples for microscopy (including stains for pneumocystis) and culture (bacterial, fungal, and mycobacterial), viruses, and PCR.
- *Pleural aspiration*: cell count, protein, microscopy and culture (bacterial and mycobacterial), cytology, LDH, and pH, and pleural biopsy of all significant effusions.
- *Lung biopsy*: transbronchial, percutaneous, or open lung biopsy. Seek specialist advice.

Table 8.4 CXR patterns in HIV-associated disease

Radiological finding	Disease process
Normal	● PCP, viral pneumonia (if hypoxic on exercise)
Focal infiltrate	● Bacterial (<i>S. pneumoniae</i>, <i>H. influenzae</i>) ● Mycobacteria (TB or MAI) ● Fungal organisms (<i>Cryptococcus</i>, <i>Histoplasma capsulatum</i>, <i>Aspergillus</i>, <i>Candida</i>) ● Patients may have atypical presentations, i.e. TB presenting with lower lobe consolidation/pleural effusion, instead of upper lobe cavity ● <i>Nocardia</i> or <i>Rhodococcus equi</i> (rare) ● Pulmonary KS or lymphoma ● PCP (apical if on nebulized pentamidine prophylaxis)
Cavitating	● Bacterial (staphylococcal, streptococcal, <i>Nocardia</i>, anaerobes) ● Mycobacteria ● Fungal organisms ● PCP may produce thin-walled cysts (pneumatoceles)
Pneumothorax	● PCP: occasionally when pneumatocele ruptures ● TB
Diffuse infiltrate	● PCP, classical presentation ● Respiratory viruses (RSV, adenovirus, parainfluenza) ● CMV (often difficult to decide whether pathogenic role) ● Miliary TB ● Fungal organisms ● Toxoplasmosis ● Lymphocytic interstitial pneumonitis
Pleural effusion	● Bacterial (mainly <i>S. pneumoniae</i>) ● Mycobacteria (mainly TB) ● Lymphoma ● Heart failure ● KS
Mediastinal lymphadenopathy	● Not a feature of HIV-related lymphadenopathy ● Mycobacteria, fungal infection ● Lymphoma and KS

Respiratory emergencies in HIV-positive patients: management

General measures

- Monitor pulse, BP, and temperature regularly.
- Pulse oximetry should be used with supplementary O₂ to maintain saturations above 90%.

Assisted ventilation

Being HIV-infected is not, in itself, a contraindication to assisted ventilation or intensive care. Indeed, many acute respiratory infections requiring such support achieve excellent outcomes. It is the individual's stage of disease and general prognosis that deem such management appropriate or inappropriate, as well as the views of the patient and their next of kin.

Specific treatment of respiratory conditions

(See Table 8.5.) Contact local microbiology or ID services if uncertain.

Table 8.5 Suggested treatment of respiratory conditions

Condition	Treatment
CAP (CD4 count >200 cells/mm ³)	Co-amoxiclav IV/PO or ceftriaxone 2g od IV for 5–7 days <i>plus</i> azithromycin 500mg od IV/PO for 3 days
CAP (CD4 count <200 cells/mm ³)	Treat as per CAP for patients with CD4 count >200, but in addition, if there is any suggestion of PCP, treat as PCP as well
PCP (if PaO ₂ <9.3kPa, add prednisolone 40mg bd PO for 5 days, then 40mg od for 5 days, then 20mg od for 10 days)	● First line: Co-trimoxazole 120mg/kg in four divided doses IV/PO for 21 days (Before commencing co-trimoxazole, G6PD levels should be checked, but treatment should not be delayed while awaiting the result) ● Second line: Clindamycin 600mg–1.2g qds PO/IV + primaquine 15–30mg od PO for 14–21 days (not for G6PD-deficient patients) <i>or</i> Pentamidine isetionate 4mg/kg od IV for 14–21 days (3-day 'crossover period' is required if changing from first line to second line) <i>or</i> atovaquone 750mg PO bd for 21 days
Hospital-acquired pneumonia	Ceftazidime 2g tds IV <i>or</i> ciprofloxacin 500mg bd PO/IV for 5 days
Neutropenic patient (duration of treatment guided by microbiologist)	If any suggestion of PCP, treat as PCP <i>plus</i> Piperacillin–tazobactam 4.5g tds IV for 7–14 days + azithromycin 500mg od IV/PO <i>plus</i> Gentamicin (5mg/kg IV according to levels)
KS	HAART + chemotherapy
Lymphoma	HAART + chemotherapy

Treatment of aspergillosis, other fungi, nocardiosis, and CMV pneumonitis should be undertaken by clinicians experienced in the use of antimicrobials for these pathogens, given their increased toxicity and drug–drug interactions.

Gastrointestinal presentations in HIV-positive patients: assessment

Opportunistic infections, malignancies, and antiretroviral drug toxicity can all frequently manifest as symptoms/signs in the GIT.

Key symptoms and signs

- **General:** assess hydration, weight, and nutritional status.
- **Diarrhoea:** can be caused by multiple pathogens (both common and opportunistic) (see Table 8.5), drug therapy, or advanced HIV per se. The presence of associated symptoms (fever, abdominal pain, blood PR) should be established. An awareness of the CD4 count will assist in directing management.
- **Weight loss:** can be caused by advanced HIV infection, may be the result of chronic diarrhoea/malabsorption, may be the presenting symptom of an underlying malignancy or opportunistic infection, or may represent toxicity to antiretroviral therapy (particularly subcutaneous fat loss).
- **Abdominal pain:** can be a feature of GI infections (see Table 8.5), biliary tree disease, or pancreatitis—which may be drug-induced, notably by nucleoside analogues, particularly didanosine. Lactic acidosis and hepatic steatosis are rare complications of antiretroviral therapy that may present as vague abdominal pain.
- **Loin pain/nephrolithiasis:** is a well-recognized side effect of indinavir therapy. Stones are unlikely to be seen on plain X-rays and usually respond to conservative management with fluid input, without the need to discontinue the offending agent. With severe episodes (haematuria and confirmed calculi on renal tract investigation), change therapy as there is a risk of further episodes and progressive renal damage.
- **Jaundice:** may be the result of viral hepatitis (acute or chronic), biliary tract disease, drug-induced hepatitis, or hepatic involvement by other opportunistic infections or tumours. Also associated with atazanavir where, for this specific drug, the development of unconjugated hyperbilirubinaemia may occur in susceptible individuals who have minor abnormalities of the bile acid transporter genes (e.g. MDR). It is a benign side effect but can cause significant jaundice in some patients.
- **Dysphagia:** is most commonly caused by candidal infection (oral *Candida* is usually present), and less commonly by ulceration secondary to HSV, VZV, CMV, or idiopathic (aphthous).
- **Oral lesions:** oral *Candida* (usually in a pseudomembranous form, appearing as white plaques, but may be erythematous or hyperplastic) and oral hairy leukoplakia (white plaques on the side of the tongue) are common signs in individuals with HIV infection and may be the first presenting features of advancing infection. KS may present as red/purple macules on the palate or gingival margin. Oral chancres of primary syphilis may occasionally be seen, in MSM more frequently than in heterosexual patients.

Practice points

There is an epidemic of acute hepatitis C and syphilis in sexually active men who have sex with men in the UK. Always test for these organisms if there are concerns or symptoms.

Gastrointestinal presentations in HIV-positive patients: investigations

General investigations

- *FBC, U&Es, LFTs, CRP*: check for evidence of anaemia, dehydration, and hepatic dysfunction.
- *Blood cultures*: bacterial GI infections are more likely to be accompanied by systemic infection in the immunocompromised host. Mycobacterial blood cultures (particularly considering atypical mycobacteria in individuals with CD4 counts <100 cells/mm³).
- *Amylase*: check for pancreatitis in individuals with abdominal pain.
- *Uncuffed serum lactate*: consider the possibility of lactic acidosis in the unwell patient receiving antiretroviral therapy with non-specific abdominal symptoms. Send to a lab rapidly for an accurate result.
- *Hepatitis serology*: consider acute hepatitis A/B/E (or hepatitis D super-infection if already HBV-positive) in the jaundiced patient and chronic hepatitis B/C in patients with evidence of chronic liver disease. New onset of abnormal LFTs may be due to hepatitis C.
- *Syphilis serology*.
- *Rectal/genital STI swabs*: send swabs for *Chlamydia*/LGV/gonorrhoea if there are rectal/lower GI symptoms.

Specific investigations

- *Stool specimens*: should be examined/cultured for bacteria and ova, cysts, and parasites. At least three stool specimens should be sent. *Clostridium difficile* toxin should be requested in individuals who have taken or are taking antibiotics. In an individual with severe immunosuppression (CD4 count <100 cells/mm³) and negative conventional stool analysis, examination for microsporidial species should be performed.
- *AXR*: look for evidence of toxic dilatation in the patient presenting with diarrhoea/abdominal pain. The major causes are CMV (with CD4 count <100 cells/mm³) and bacterial infections (*Salmonella*, *Shigella*, *Campylobacter*) at higher CD4 counts.
- *USS*: look for evidence of hepatic/biliary abnormality in patients with jaundice/abnormal LFTs, evidence of ascites in patients with abdominal distension, and abdominal masses/lymphadenopathy in individuals with opportunistic infections/tumours.
- *CT scanning*: look for evidence of masses/lymphadenopathy in individuals with abdominal pain, which may represent involvement by underlying opportunistic infections or tumours.
- *Upper GI endoscopy*: look for oesophageal lesions in patients with dysphagia and gastric lesions in patients with abdominal pain. Perform duodenal biopsies in individuals with chronic diarrhoea where no pathogen has been isolated.
- *Sigmoidoscopy/colonoscopy*: look for evidence of involvement by opportunistic pathogens/tumours in patients with chronic diarrhoea or abdominal pain. Rectal/colonic biopsies should be performed in patients with chronic diarrhoea where no pathogen has been isolated.
- *ERCP/MRCP*: should be considered in individuals with evidence of obstructive jaundice where no cause has been found, or in individuals with chronic abdominal pain looking for any evidence of ascending cholangitis.

Gastrointestinal presentations in HIV-positive patients: management

- General principles of rehydration, analgesia, and nutritional support should apply.
- If the CD4 count is >200 cells/mm³, patients are usually treated in a similar way to HIV-seronegative individuals.
- Specific therapy should be directed towards the suspected/proven underlying cause (see Table 8.6). Consider empiric treatment with antibacterial agents for acute diarrhoea where a bacterial cause is likely. This should be treated according to sensitivities and local protocol, unless the patient is compromised. In the unwell patient with diarrhoea, consider additional anti-CMV therapy (usually ganciclovir) if the CD4 count is <100 cells/mm³.
- Antiretroviral therapy should not be discontinued or modified without discussion with an experienced HIV clinician.

Table 8.6 GI pathogens in HIV-positive patients

Pathogen	Clinical presentation	Diagnosis	Treatment
<i>Candida</i>	Oral: usually white plaques. Usually CD4 count <350 Oesophageal: dysphagia or odynophagia. Usually CD4 count <200	Usually based upon clinical appearance Can be confirmed by biopsy/culture	Oral: usually with fluconazole (50mg × 5 days) or 400mg stat Oesophageal: fluconazole 100mg od × 14 days Alternative agents may be recommended in cases of suspected/proven 'azole' resistance
<i>Salmonella</i>	Diarrhoea ± fever, abdominal pain, and blood PR; colonic dilatation ± any CD4 count	Confirmed by stool (± blood) cultures Empiric treatment may be considered in the unwell patient	Ciprofloxacin 500mg bd × 7–14 days Cephalosporin if ciprofloxacin-intolerant or resistant
<i>Shigella</i>	Diarrhoea ± fever; abdominal pain, and blood PR; colonic dilatation ± any CD4 count	Confirmed by stool (± blood) cultures Empiric treatment may be considered in the unwell patient	Ciprofloxacin 500mg bd × 7–14 days Trimethoprim if ciprofloxacin-intolerant or resistant
<i>Campylobacter</i>	Diarrhoea ± fever, abdominal pain, and blood PR; colonic dilatation ± any CD4 count	Confirmed by stool (± blood) cultures Empiric treatment may be considered in the unwell patient	Ciprofloxacin 500mg bd × 7–14 days Azithromycin if ciprofloxacin-intolerant or resistant
Cryptosporidia	May present acutely as 'traveller's diarrhoea' at any CD4 count which usually clears spontaneously, or chronically as watery diarrhoea with CD4 count <100	Demonstration of organism on stool analysis and/or biopsy	No proven effective antimicrobial therapy (consider nitazoxanide). Acute cryptosporidial infection usually resolves spontaneously; treat chronic infection with HAART
Microsporidia	Watery diarrhoea in individuals with CD4 count <100	Demonstration of organisms by specific stool analysis or on biopsy/electron microscopy	Albendazole is beneficial in some studies. Effective HIV treatment results in clinical improvement

<i>Isospora</i>	Watery diarrhoea in individuals with CD4 count <100	AFB smear of stool	Co-trimoxazole usually effective
<i>Entamoeba histolytica</i>	Diarrhoea ± blood and abdominal pain. Any CD4 count	Ova, cysts, and parasites of stool	Metronidazole 800mg tds or tinidazole, then diloxanide
<i>Giardia</i>	Watery diarrhoea. Any CD4 count	Ova, cysts, and parasites of stool	Metronidazole 400mg tds for 10 days or tinidazole 2g PO on days 1 and 5
CMV	Oesophageal: dysphagia with ulceration Gastric/upper GI: abdominal pain Colonic: diarrhoea ± abdominal pain. Toxic dilatation may occur. CD4 <100	Demonstration of organisms by immunocytochemistry of biopsy specimens	Specific CMV therapy (usually ganciclovir 5mg/kg bd for 3–4 weeks). Effective anti-HIV therapy should reduce risk of recurrence/other end-organ disease
Herpes simplex	Oesophageal ulceration, or proctitis/colitis	Demonstration of organisms on biopsy/culture	Aciclovir 200–800mg 5x/day or 5mg/kg IV for 2–3 weeks
Herpes zoster	Oesophageal ulceration	Demonstration of organisms on biopsy/culture	Aciclovir 400–800mg 5x/day or 5–10mg/kg IV for 2–3 weeks
<i>Mycobacterium avium</i> complex	Chronic, watery diarrhoea ± abdominal pain. Usually systemic symptoms (fever, weight loss, pancytopenia). CD4 count <50	Blood cultures (specific mycobacterial culture: may take several weeks) or demonstration of organisms on biopsy	Three agents (usually rifabutin, ethambutol, and clarithromycin or azithromycin) Effective anti-HIV therapy is associated with clinical response
<i>Clostridium difficile</i>	Watery diarrhoea. History of antibiotics Any CD4 count	Stool toxin assay	Stop culprit antibiotic(s) if possible Metronidazole 400mg tds PO–10 days Vancomycin 125mg qds x 10 days

Pyrexia of unknown origin

Assessment

- Look for signs/symptoms of focal infection.
- Check for neutropenia.
- Consider TB.
- Consider line sepsis if indwelling IV cannulae.
- Consider drug-related fever (detailed drug history, including antiretroviral agents).
- Consider underlying lymphoma.
- Detailed travel history is essential.

Investigations

- Usual investigation of fever.
- CrAg.
- Mycobacterial blood cultures (MAI if CD4 count <100 cells/mm³).
- Consider:
 - CT scan head.
 - CT scan chest and abdomen.
 - Lymph node biopsy (if significant lymphadenopathy).
 - Bone marrow examination.
 - Fludeoxyglucose positron emission tomography (FDG-PET) CT body.

Treatment

- Unless clinically unwell, most clinicians would recommend withholding empiric antimicrobial therapy.
- Specific antimicrobial (or other) therapy should be directed against the suspected underlying pathogen/process.

Immune reconstitution inflammatory syndrome

- Immune reconstitution inflammatory syndrome (IRIS) may be seen, following the commencement of antiretroviral therapy in patients with HIV. It is characterized by an inflammatory response associated with worsening of pre-existing infections. These infections may have been previously diagnosed and treated or may be unmasked by the patient's regained ability to mount an inflammatory response.
- This inflammatory reaction is usually self-limited, particularly when the pre-existing infection is effectively treated. However, long-term complications and adverse outcomes may rarely be seen, particularly in patients with neurological involvement.
- The clinical features of IRIS are highly variable, but the most common presentations are with fever and lymphadenopathy. The main risk factors for IRIS are a low baseline CD4 count and/or a rapid recovery of CD4 and a rapid fall in viral load after initiation of HAART. Most patients with IRIS develop symptoms within 7 days to a few months after initiation of antiretroviral treatment.
- In order to reduce the likelihood of IRIS, antiretroviral therapy may be delayed for 1–2 months while treating a known opportunistic infection with the appropriate antimicrobial. Antiretroviral therapy should only be delayed for about 2 weeks in patients infected with *M. tuberculosis* who have a CD4 cell count <100 cells/mm³.
- IRIS is generally a diagnosis of exclusion. The possibility of drug reaction or resistance, patient non-compliance, and persistently active infection should be excluded first. For example, abacavir hypersensitivity may be confused with IRIS, but symptoms are exacerbated following each dose of abacavir.
- When IRIS is thought to be highly likely, further invasive diagnostic procedures to find an occult infection may be delayed. Start or continue to treat the underlying pathogen in patients with IRIS. Continue antiretroviral therapy in most patients, except for cases when the presentation of IRIS is life- or organ-threatening. Steroids may reduce the inflammatory response in some cases. When it is decided to use steroids, prednisolone or methylprednisolone may be given initially at a daily dose of 1–1.5mg/kg (60–80mg) and then tapered, while monitoring for recurrence of clinical symptoms, over weeks to months.

Dermatological presentations

- Seroconversion can present with a viral exanthematous rash.
- Consider drug-related causes (including antiretroviral agents), but do not discontinue antiretroviral agents (unless essential) without discussion with an HIV clinician.
- In particular, patients recently having commenced nevirapine therapy may be at risk of Stevens–Johnson syndrome or toxic epidermal necrolysis, and patients having recently commenced abacavir may be at risk of a hypersensitivity syndrome (⚡ Antiretroviral toxicity, pp. 538–9). Milder rashes are common after initiation of any antiretroviral and usually self-limiting, and usually HAART can be continued with an antihistamine for symptom control.
- Most dermatological complaints can behave atypically and more severely in individuals with HIV infection:
 - Shingles (varicella-zoster) may present with multi-dermatomal lesions and/or neurological involvement.
 - Herpes simplex may present with more severe lesions, more frequent recurrences, or prolonged outbreaks. There may also be neurological involvement, requiring higher doses of aciclovir than used in immunocompetent patients.
 - Seborrhoeic dermatitis may present more aggressively in the HIV-positive patient and may be recalcitrant to conventional therapy.
 - Early syphilis should be considered in *any* HIV-positive patient with dermatological lesions.

Haematological presentations

Cytopenias may be the result of HIV infection per se, antiretroviral (or other drug) toxicity, or bone marrow involvement by opportunistic infections or tumours.

- Mild to moderate thrombocytopenia is a common finding in the HIV-infected patient; a severe idiopathic thrombocytopenic purpura (ITP) picture is well recognized. Usually responds to antiretroviral therapy, but steroids/Ig may be required in severe cases.
- Anaemia is a recognized side effect of antiretroviral therapy—notably zidovudine (AZT) therapy.
- Neutropenia is a recognized side effect of zidovudine (AZT) and ganciclovir therapy, and occurs more frequently in the HIV-infected patient receiving chemotherapy for malignancy. Standard management of neutropenia should apply.

Antiretroviral toxicity

- Newer agents tend to be less toxic than older agents (such as zidovudine, didanosine, and stavudine), which are now less commonly used.
- Many clinicians are unfamiliar with the agents used to treat HIV infection. They are associated with multiple toxicities, some of which may present to the emergency clinician. Always consider discussing the case with a clinician experienced in the use and toxicity of these drugs.
- The key principles of management are to recognize the possibility of iatrogenic illness and to exert caution in management. In order to minimize the risk of development of resistance and to preserve future treatment options, antiretroviral agents should be discontinued only in discussion with an HIV clinician. If necessary, the toxic agent is switched and the withdrawal of one or two of a combination of agents (thus leaving an individual on suboptimal therapy) should be avoided.
- In individuals receiving antiretroviral therapy who present systemically unwell, the possibility of lactic acidosis should always be considered (see  Mitochondrial toxicity, pp. 538–9).

Rash and hypersensitivity

- Abacavir hypersensitivity reaction (4%) can present as a fever or maculopapular rash (usually in the first 2 months of treatment), often associated with one or more other symptoms or signs (fever, sore throat, GI or respiratory symptoms, laboratory abnormalities). If strongly suspected, abacavir should be discontinued and the patient never rechallenged (risk of fatal hypersensitivity reaction). This decision should be taken by an experienced HIV clinician. Most clinicians now use the HLA-B*57:01 test to predict the likelihood of abacavir hypersensitivity (90% risk).
- Non-nucleoside reverse transcriptase inhibitors (efavirenz and nevirapine): maculopapular rash (~10%), peaking at 2 weeks, often associated with abnormal LFTs. Sometimes can be 'pushed through' with antihistamines (cetirizine) but needs close monitoring (associated severe or life-threatening hepatotoxicity not uncommon). Stevens–Johnson syndrome and toxic epidermal necrolysis are well recognized, but uncommon, side effects of nevirapine. Stevens–Johnson syndrome is more common in patients who start treatment with high CD4 counts. Nevirapine should not be used in patients with a high CD4 count, as it increases the risk of Stevens–Johnson syndrome.

Mitochondrial toxicity

Usually attributed to the unwanted inhibition of mitochondrial DNA polymerase gamma by nucleoside reverse transcriptase inhibitors (particularly stavudine and didanosine). Over months, this can lead to mitochondrial dysfunction which can manifest as:

- Lactic acidosis/hepatic steatosis resulting from general mitochondrial dysfunction. If suspected (general malaise, abdominal pain, metabolic acidosis, abnormal LFTs), an uncuffed blood sample should be sent for immediate lactate measurement, and if high ($>5\text{mmol/L}$) with associated acidosis, the offending drug(s) stopped. This condition can be rapidly fatal, and admission to ICU is occasionally required.

- Acute pancreatitis: particularly associated with didanosine (ddl) (also precipitated by alcohol, gallstones, pentamidine, and some opportunistic infections).
- Myopathy (muscle biopsy diagnostic): zidovudine (AZT).
- Antiretroviral-induced peripheral neuropathy: particularly associated with zalcitabine, stavudine, and didanosine.
- Renal tubular acidosis/Fanconi's syndrome has been rarely reported with tenofovir.

Metabolic disturbances

Hyperlipidaemia and glucose intolerance (including frank diabetes) have been associated with the use of antiretroviral therapy, particularly protease inhibitors. The association with premature cardiovascular disease currently remains uncertain but is suggested by some cohort studies. The prescription of statins in this patient group should be made with care, given the potential drug–drug interactions; simvastatin is contraindicated in patients receiving protease inhibitors (pravastatin or atorvastatin are preferred).

Haematological toxicity

Nucleoside analogues—particularly zidovudine (AZT)—are associated with haematological toxicity, especially anaemia and neutropenia, which usually occurs during the first few weeks/months of therapy.

Hepatotoxicity

All of the available antiretroviral agents have been associated with hepatotoxicity, particularly in those individuals co-infected with hepatitis C/B. Nevirapine has been rarely associated with fulminant hepatitis (within the first 6 weeks of therapy). Hepatic steatosis (as part of a syndrome of mitochondrial dysfunction—as outlined earlier) is a well-recognized, though rare, complication of nucleoside analogue therapy. Most HIV physicians would closely monitor LFTs without discontinuation, unless there is evidence of clinical hepatitis or an ALT/AST of >5–10 times the upper limit of normal.

Neurological toxicity

Efavirenz (and occasionally nevirapine) can cause significant neuropsychiatric disease. In the majority of patients, this occurs in the first 4 weeks of therapy and can present as mood swings or depression. Treatment is discontinued in 5–10% of individuals, though up to 50% will experience some symptoms of 'muzzy head' or nightmares.

Practice points

Always discuss treatment initiation/change with an experienced HIV clinician. Do not stop antiretroviral therapy without discussion with an experienced HIV clinician.

Drug interactions with antiretroviral therapy

Protease inhibitors and non-nucleoside reverse transcriptase inhibitors are metabolized through the cytochrome P450 system and exhibit a wide variety of drug interactions, many of which have potentially serious consequences. It is recommended that co-administration of other P450-mediated agents should be with caution.

Further information is available in the *BNF* or can be accessed via the University of Liverpool website at  <https://www.hiv-druginteractions.org>

Post-exposure prophylaxis

Evidence that PEP may be effective can be drawn from both animal and vertical transmission studies. The most compelling data are from a case-controlled study of health-care workers where the administration of zidovudine (AZT) monotherapy was shown to be associated with ~80% reduction in HIV transmission.

Most hospitals/emergency departments will have established protocols for the management of PEP (see Box 8.4). However, the following general principles apply:

- The risk of HIV transmission is the product of the risk of the 'donor' being HIV-positive and the risk of HIV infection from the exposure.
- To estimate the risk of the donor being HIV-positive, an understanding of the epidemiology of the 'risk group' of the individual is helpful.
 - For example, the risk of a sexually active homosexual man in the UK being HIV-positive is estimated at ~12.5% in London and 5.9% across the UK as a whole.
 - The risk of an IVDU being HIV-positive is <1.1%.
 - The risk of a heterosexual being HIV-positive requires knowledge of the HIV prevalence in the country in which they have been sexually active (as high as 20–50% in some sub-Saharan African countries). In the black African population in the UK, prevalence has been estimated at 4.1% among men and 7.1% among women.

Inoculation injuries

The risk of HIV transmission from exposures has been estimated at:

- Needle-stick injury: 1 in 333.
- Splash injury (to eyes or diseased skin): <1 in 1000.
- Human bite: <1 in 10 000 (PEP not recommended).
- Injury from discarded sharps in the community: risk usually low, as HIV becomes non-viable after a few hours and the use of the sharps prior to being discarded is usually unknown.

NB Do not forget that optimal management of sharps injuries includes immediate wound management (bleeding and simple washing) and consideration of exposure to hepatitis B (assess vaccination status and consider accelerated vaccination or Ig) and hepatitis C.

Sexual exposure

The risk of HIV transmission through sexual exposure from a known HIV-positive individual not on HAART is estimated at:

- Unprotected receptive vaginal sex (♂ to ♀): 1 in 1000.
- Unprotected insertive vaginal sex (♀ to ♂): 1 in 1219.
- Unprotected anal sex (risk to insertive partner): 1 in 666.
- Unprotected anal sex (risk to receptive partner): 1 in 90.
- Oral sex with ejaculation (both receptive and insertive): <1 in 10 000.

Factors associated with increased risk include

- *Donor*: advanced HIV infection; high viral load.
- *Injury*: hollow-bore needle; insertion of needle into artery or vein of the patient; visible blood on device; deep injury.

Following assessment of the risk, consider PEP.

Given the potential opportunities for future risk reduction and concerns regarding PEP efficacy, HIV resistance, and drug toxicity in this setting, it is recommended that the decision to administer PEP after sexual exposure is taken in conjunction with clinicians experienced in GUM/HIV medicine.

More guidance can be found at  <https://www.bashhguidelines.org/media/1027/pepse-2015.pdf>

Box 8.4 Post-exposure prophylaxis (PEP)

- A risk assessment should be carried out first. For occupational exposures, the risk assessment is carried out by occupational health (A&E if out of hours). If the risk of infection is considered significant, PEP should be commenced as early as possible, ideally within 1h (and generally within 72h after the exposure), and continued for 28 days.
- The following regimen is now recommended for PEP (for occupational and non-occupational use) for 28 days:
 - *One Truvada® tablet [245mg tenofovir disoproxil (as fumarate) and 200mg emtricitabine (FTC)] once a day, plus*
 - *One raltegravir tablet (400mg) twice a day.*

Notes

- Report blood and body fluid exposure incidents to the occupational health department to arrange immediate assessment or, if out of hours, attend the A&E department. Follow-up is carried out by occupational health.
- Due to the sensitivity of the issue, the source patient should not be approached by the exposed member of staff. Occupational health (or A&E if out of hours) will arrange this test.

Diabetes and endocrine emergencies

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Diabetic ketoacidosis: assessment

DKA predominantly occurs in patients with type 1 diabetes mellitus (T1DM) and insulin-dependent type 2 diabetes mellitus (T2DM). It is also being increasingly recognized in the initial presentation of an atypical form of T2DM in non-white patients known as ketosis-prone T2DM where there is a severe, transient defect in insulin secretion.

Clinical features

These include:

- Polyuria and polydipsia; patients become dehydrated over a few days.
- Weight loss, weakness.
- Hyperventilation or breathlessness; the acidosis causes Kussmaul's respiration (a deep sighing respiration).
- Abdominal pain: DKA may present as an 'acute abdomen'.
- Vomiting: exacerbates dehydration.
- Confusion, coma occurs in 10%.
- On examination, pay attention to the haemodynamic stability, state of hydration, ventilation rate, level of consciousness, and septic foci.

Investigations

- *Blood glucose* Assess capillary and venous blood glucose. This need not be very high (≥ 11 mmol/L) (see 'Note' below).
- *Venous gas* Assess the degree of acidosis (see 'Note' below).
- *U&E, Mg²⁺* Assess serum K⁺ and renal function.

$$\text{Corrected Na}^+ = \text{Na}^+ + 1.6 \times [(\text{plasma glucose} - 55)/5.5]$$

$$\text{Serum osmolality} = 2 \times (\text{Na}^+) + \text{urea} + \text{glucose}$$
- *Urinalysis* Ketones strongly positive ($\geq 2+$) (see 'Note' below).
- *Urinary HCG* Exclude pregnancy in ♀ of childbearing potential.
- *FBC* WBC may be elevated (neutrophilia): a leukaemoid reaction can occur in absence of infection.
- *Septic screen* Urine and blood cultures.
- *Plasma ketones* Ketones elevated (≥ 3 mmol/L) (see 'Note' below).
- *CXR* Look specifically for any infection.
- *Amylase* May be high, with abdominal pain and vomiting, in absence of pancreatitis. Acute pancreatitis may occur in 7–10% of patients with DKA (often in association with hypertriglyceridaemia).

Note

- Diagnosis of DKA requires all three of:
 - Blood glucose ≥ 11 mmol/L.
 - Ketonaemia ≥ 3 mmol/L ($\geq 2+$ on urinalysis).
 - Metabolic acidosis with venous or arterial pH ≤ 7.30 and/or serum bicarbonate ≤ 15 mmol/L.
- Consider hyperosmolar hyperglycaemic syndrome (HHS)
 - ➡ Hyperosmolar hyperglycaemic syndrome, pp. 552–3) and other causes of hyperglycaemia/acidosis, e.g. aspirin OD and lactic acidosis.

- Severe acidaemia can be present with glucose values as low as 11mmol/L if the patient has recently taken insulin (as this alone is insufficient to correct the acidosis in the presence of dehydration) or is managed using an SC insulin pump (where ketosis can develop rapidly if infusion of insulin via the insulin pump fails).
- Plasma ketones should be measured using bedside ketone meters, if available.
- Ketones may be present in normal individuals after a period of starvation.
- False-positive ketones on urinalysis can occur with certain drugs (e.g. levodopa, phenazopyrazine, valproic acid, vitamin C). If in doubt, assess plasma ketones.
- Venous blood gas is sufficient, unless clinical need to monitor pO_2 / pCO_2 level in patients.

Common precipitants of DKA

- Infections: 30%.
- Non-compliance with treatment: 20%.
- Newly diagnosed DM: 25%.
- Surgical abdomen/pancreatitis: 10%.

Poor prognostic features in DKA

Consider HDU management, central venous access, excluding a surgical cause, and early liaison with ITU when:

- Oxygen saturations <92%.
- SBP <90mmHg, or pulse >100 or <60bpm.
- GCS score <12.
- Oliguria.
- pH <7.0 or serum bicarbonate <5mmol/L or ketones >6mmol/L.
- Hypokalaemia on admission (K^+ <3.5mmol/L).
- Lactate >6.
- Anion gap >16.
- Serum osmolality >320.
- Significant comorbidities, e.g. cardiac failure, renal failure.
- Worsening acidosis/ketonaemia despite treatment.

DKA: management

General measures

- Initiate rehydration and fixed-dose IV insulin therapy without delay.
- Site two IV cannulae: one in each arm (one for 0.9% saline and one for insulin $\pm$ glucose). Start fluid replacement (see  Fluid replacement, p. 548).
- Consider a central line in patients with poor prognostic features.
- NBM for at least 6h (gastroparesis is common).
- NG tube: if there is impaired conscious level, to prevent vomiting and aspiration.
- Urinary catheter if oliguria is present or serum creatinine is high.
- Broad-spectrum antibiotics if infection suspected.
- Prophylactic-dose LMWH should be given unless contraindicated.
- Some patients may require monitoring on an ECG for T-wave changes during treatment.
- Monitor blood glucose, capillary ketones, and urine output hourly.
- Venous blood gas (pH, bicarbonate K^+) at 0, 4, 6, 12, and 18h and before stopping the fixed-rate insulin regimen.
- U&Es at 0, 6, 12, and 24h (Mg^{2+} levels should be monitored daily).

Fluid replacement

Use normal (0.9%) saline to replace the fluid deficit. The average fluid loss in DKA is 100mL/kg. (More cautious fluid replacement is needed for patients with cardiac and renal disease, elderly patients, young patients aged 18–25 years, and pregnant patients.)

- 1L of 0.9% saline over 1h*.
- 1L of 0.9% saline over 2h $\times$ 2*.
- 1L of 0.9% saline over 4h $\times$ 2*.
- 1L of 0.9% saline over 6h*.
- If SBP <90mmHg, give 500mL of 0.9% saline IV over 15–20min. Repeat further if SBP <100mmHg. If poor response, consider septic shock or cardiac failure. Central venous monitoring needed to guide further fluid management.
- When blood glucose reaches ≤ 14 mmol/L, IV 10% glucose is given at 125mL/h concurrently with 0.9% saline (through an IV cannula in the other arm). Consider reducing 0.9% saline infusion if risk of overload.
- Use of bicarbonate is not recommended routinely.

Potassium replacement

Total body K^+ is depleted, and plasma K^+ level falls rapidly as K^+ shifts into cells under the action of insulin. Do not give potassium chloride (KCl) in the first litre or if serum K^+ is >5.5 mmol/L. All subsequent fluid for the next 24h should contain KCl, unless the urine output is <30 mL/h or serum K^+ remains in excess of 5.5mmol/L (see Table 9.1).

Insulin replacement

The only indication for delaying insulin is a serum K^+ level of <3.3 mmol/L, as insulin will worsen hypokalaemia by driving K^+ into cells. Patients with an

* Plus K^+ replacement; see  Potassium replacement, p. 548

initial serum K^+ level of $<3.3\text{mmol/L}$ should receive fluid and K^+ replacement prior to insulin.

- Start an IV insulin infusion with 50U of soluble insulin added to 50mL of 0.9% saline delivered via a syringe driver.
- *High-dose fixed-rate* IV insulin is infused at 0.1U/kg/h , e.g. for an 80-kg man, give 8U/h until exit criteria (see  Exit criteria and cessation of IV insulin, p. 549).
- SC basal (long-acting) insulin should be continued at the usual dose, alongside the high-dose fixed-rate IV insulin infusion.
- The response to insulin infusion is reviewed after 1h. If blood glucose is not dropping by 3mmol/h and capillary ketones by 0.5mmol/L , the infusion rate is $\uparrow$ by 1U/h . The increase in insulin infusion rate may be repeated hourly, if necessary, to achieve a reduction in blood glucose and capillary ketones. Urinary ketones may take a little longer to clear.

Exit criteria and cessation of IV insulin

- The fixed-rate insulin is continued until capillary ketones are $<0.6\text{mmol/L}$ and venous bicarbonate is >15 . At this point, if the patient is eating and drinking regularly, stop the IV insulin pump 30–60min after rapid-acting insulin with meal.
- SC basal insulin should have been continued on admission, but if stopped in error, give prior to discontinuing IV insulin as the half-life of IV insulin is short and *continued* replacement (IV or SC) is essential.
- If the patient is not eating and drinking or if severe sepsis or ACS, change to variable-rate insulin infusion (see Table 9.2).
- Ensure a review by the specialist diabetes team has taken place within 24h of admission.

Table 9.1 Suggested regimen for potassium supplementation

Plasma K^+ (mmol/L)	Amount of K^+ (mmol) to add to each litre of fluid
>5.50	Nil
$3.5\text{--}5.5$	40
<3.5	Seek advice from senior or specialist*

* Additional K^+ may be needed (e.g. 40mmol in 100mL of 0.9% saline over 2h) via a central line in HDU.

Table 9.2 Example of variable-rate insulin infusion prescription

Blood glucose (hourly) (mmol/L)	Insulin infusion (U/h)
<4.0	0.5
$4.1\text{--}7.0$	1
$7.1\text{--}9.0$	2
$9.1\text{--}11.0$	3
$11.1\text{--}14.0$	4
$14.1\text{--}17$	5
$17.1\text{--}20$	6
>20.0	6—call doctor

DKA: targets and complications

Biochemical targets

Remember, rapid normalization of biochemistry can be detrimental in any patient. It is wiser to be cautious and suboptimal than enthusiastic and dangerous.

- Reduce capillary blood glucose by 3mmol/L per hour.
- Increase venous bicarbonate by 3mmol/L per hour.
- Reduce plasma ketone concentration by 0.5mmol/L per hour.

Complications

(See Box 9.1.)

- Avoid *hypoglycaemia* or *hypokalaemia* from overzealous insulin replacement.
- *Cerebral oedema* occurs mainly in children. It may be precipitated by sudden shifts in plasma osmolality during treatment. Symptoms include drowsiness, severe headache, confusion. Treat as described under ☞ Raised intracranial pressure, pp. 388–90. Give IV mannitol 0.5g/kg body weight, repeated as necessary. Restrict IV fluids and move to ITU. Mortality is 70%; recovery of normal function is only 7–14%.
- Serum PO_4^{3-} falls during treatment, as it moves intracellularly with K^+ . PO_4^{3-} levels do not need to be routinely monitored, but consider assessment in presence of respiratory or skeletal weakness. If the PO_4^{3-} level is $<0.3\text{mmol/L}$, give PO_4^{3-} IV (monobasic potassium phosphate infused at a maximum rate of 9mmol every 12h). Check preparations with your pharmacy. Monitor Ca^{2+} levels during the infusion.
- Serum Mg^{2+} may fall during insulin therapy. If Mg^{2+} levels fall to $<0.5\text{mmol/L}$, give 4–8mmol (2mL of 50%) magnesium sulfate over 15–30min in 50mL of normal saline. Repeat as necessary.
- *Hyperchloraemic acidosis* (normal anion gap acidosis in a well-hydrated patient) may be seen with excessive administration of saline and in consumption of bicarbonate. No specific treatment is required.
- Tissue hypoperfusion results from dehydration and may trigger the coagulation cascade and result in *thromboembolism*. Use LWMH (e.g. enoxaparin SC) for prophylaxis.

Box 9.1 Complications of DKA

- Hypokalaemia.
- Hypophosphataemia.
- Hyperchloraemic acidosis.
- Hypoglycaemia.
- Cerebral oedema in children.
- Thromboembolism.

DKA: management key points

(See Box 9.2.)

Box 9.2 Management key points: DKA

- Consider HDU/ICU input, central line, and urinary catheter if severe acidosis, hypotension, oliguria, or other poor prognostic features.
- *Fluids*: 0.9% saline over 1h. Then: 1L 2-hourly $\times$ 2, followed by 1L 4-hourly $\times$ 2, and then 1L 6-hourly. If SBP <90 mmHg, give 1L of 0.9% saline IV over 15–20min. IV 10% glucose is started in conjunction with 0.9% saline at a rate of 125mL/h when blood glucose is <14 mmol/L.
- *Fixed high-dose IV insulin*: 50U of soluble insulin in 50mL of normal saline—start at 0.1U/kg/h. Continue SC basal (long-acting) insulin at usual dose. Continue IV insulin infusion until capillary ketones <0.6 mmol/L and venous bicarbonate >15 . At this point, if the patient is able to eat and drink, change to SC insulin regimen. If not, change to IV sliding scale. Do not stop insulin infusion until 30–60min after rapid-acting insulin with meal.
- K^+ replacement (start in the second bag of fluid). Adjust the amount of K^+ added to fluids, according to plasma K^+ .
- Monitor blood glucose, capillary ketones, and urine output hourly. Venous blood gas (pH, bicarbonate, K^+) at 0, 4, 6, 12, and 18h and before stopping the fixed-rate insulin regimen. U&Es at 0, 6, 12, and 24h (Mg^{2+} levels should be monitored daily).
- Broad-spectrum antibiotics if infection suspected.
- Thromboprophylaxis.
- NBM for at least 6h (gastroparesis is common).
- NG tube: if GCS score is reduced (to prevent vomiting and aspiration).
- There is no strong evidence for the use of IV bicarbonate.
- Ensure diabetes team review within 24h for specialist input and patient education.

Further reading

Joint British Diabetes Societies Inpatient Care Group (2013). *The management of diabetic ketoacidosis in adults*, 2nd edn. <https://www.diabetes.org.uk/resources-s3/2017-09/Management-of-DKA-241013.pdf>

Hyperosmolar hyperglycaemic syndrome (HHS) 1

HHS (previously known as hyperosmolar non-ketotic coma or HONK) classically occurs in elderly patients with T2DM. With a rise in early-onset T2DM, it is now appearing increasingly in younger patients. Complications from vascular thromboembolism and cerebral oedema are common. Reported mortality is as high as 33%.

Presentation

- Often occurs in the elderly, frequently with multiple comorbidities.
- Onset over many days with preceding polyuria, polydipsia, and symptoms from a precipitating cause (e.g. infection).
- Severe dehydration.
- Impaired conscious level: the degree correlates most with plasma osmolality. Coma is usually associated with an osmolality of >440 .
- The patient may present with a stroke, seizures, or MI.

Characteristic features

- Marked hyperglycaemia (30mmol/L or more).
- Without significant hyperketonaemia ($<3\text{mmol/L}$) or acidosis ($\text{pH} >7.3$, bicarbonate $>15\text{mmol/L}$).
- Osmolality 320mOsm/kg or more.
- Hypovolaemia.

Precipitants

- Infection—thorough physical examination is important.
- MI or CVA.
- GI bleed.
- Poor compliance with oral antidiabetic agents or high-sugar diet.
- Self-neglect or elder abuse.
- Drugs: steroids, diuretics, β -blockers, antihistamines.

Investigations

- *Glucose*: usually very high ($\geq 30\text{mmol/L}$).
- *U&Es*: dehydration causes a greater rise in urea than creatinine (normal ratio of creatinine:urea up to 20:1 micromol/L:mmol/L).
- *Significant hypernatraemia*: may be masked by high glucose. Hypernatraemia may appear to worsen as glucose falls.
- *ABG*: usually $\text{pH} >7.3$, serum bicarbonate $\geq 15\text{mmol/L}$. Coexisting lactic acidosis considerably worsens the prognosis.
- *Plasma osmolality*: calculated by: $[2 \times (\text{Na}^+) + \text{urea} + \text{glucose}]$; $>320\text{mOsm/kg}$ for diagnosis. Useful indicator of severity and for monitoring response to treatment.
- *FBC*: polycythaemia and leucocytosis may indicate dehydration or infection, respectively.
- *ECG*: look for MI or ischaemia.
- *CXR*: look for signs of infection.
- *Urine*: for urinalysis, ketones, and MC&S.
- *Plasma ketones*: may occur due to poor intake, but the level is usually $<4\text{mmol/L}$.
- *CT/MRI brain*: consider stroke or cerebral infection as a precipitant.

Management: general measures

The goals are to normalize plasma osmolality and blood glucose, to replace fluid and electrolyte losses, and to prevent complications.

- Manage in well-staffed acute medical unit (AMU) or HDU/ITU if concerning features.
- Rehydration is the mainstay of treatment. Cautious in the elderly.
- May need CVP monitoring to guide rehydration.
- NBM for at least 6h, and insert an NG tube in patients with impaired conscious level to prevent vomiting and aspiration.
- Urinary catheter if there is oliguria or high serum creatinine.
- Prophylactic-dose LMWH should be given unless contraindicated. Full-dose anticoagulation if ACS/VTE suspected.
- Treatment of sepsis or precipitating factors.
- High risk of feet ulceration. Examine the feet daily, and use heel protection if reduced consciousness or uncooperative.
- Monitor blood glucose, U&Es, plasma osmolality, and urine output hourly for the first 6h and 2-hourly thereafter if response satisfactory.
- Continuous pulse oximetry, and consider cardiac monitoring in high-risk patients.

Fluid replacement

The average fluid lost is 8–10L. This should be replaced cautiously over 48h, especially as most patients are elderly. Remember that 0.9% normal saline is hypotonic, relative to the patient's serum, and is therefore the fluid of choice, even with hypernatraemia.

- Aim for positive balance of 3–6L by 12h. Longer if comorbidities.
- If in doubt, replace fluid cautiously. Over-correction can lead to fluid overload, cerebral oedema, and central pontine myelinolysis.
- 1L of normal saline over the first 60min, then:
- 1L of normal saline with K^+ (see Table 9.1) every 2h $\times$ 2, then:
- 1L of normal saline with K^+ (see Table 9.1) every 6h until rehydrated (~48h).
- Monitor plasma osmolality. Best indicator of rate of change of hyperosmolar state to treatment.
- As hyperglycaemia is treated, an initial rise in Na^+ is expected. This is not an indication for hypotonic fluid. A rise in Na^+ is only a concern if plasma osmolality is not decreasing.

NB 'Corrected' serum Na^+ = measured serum Na^+ + [the increment above normal in blood glucose (in mmol/L)/2.3].

- Use 0.45% normal saline only if plasma osmolality not decreasing despite positive balance.
- Aim for rate of fall in plasma Na^+ of <10mmol/L in 24h.

HHS 2

Blood glucose and insulin

Aim for a fall in blood glucose of $<5\text{mmol/h}$. Reducing the serum glucose level acutely to below 14mmol/L may promote the development of cerebral oedema. Patients with HHS tend to be more sensitive to the effects of insulin.

- Do not start insulin, unless significant ketonaemia is present. Use low-dose IV insulin (0.05U/kg/h) only if ketonaemia (urine $>2+$ or plasma >1) or if blood glucose not falling with rehydration alone.
- Increase insulin by 1U/h if there is no fall in glucose.
- If blood glucose $<14\text{mmol/L}$, commence 5% or 10% glucose infusion at 125mL/h concurrently with normal saline; stop IV insulin, and continue to monitor blood glucose.
- If the patient is eating and drinking regularly, stop IV insulin; continue rehydration, and consider starting SC insulin with target glucose of $10\text{--}15\text{mmol/L}$. If previously on oral agents, restart on advice from the specialist diabetes team.

Poor prognostic features in HHS

Consider HDU/ITU management:

- Serum oxygen saturations $<92\%$.
- SBP <90 .
- Pulse >100 or $<60\text{bpm}$.
- GCS score <12 .
- Oliguria.
- Hypothermia.
- $\text{K}^+ <3.5\text{mmol/L}$ or $>6\text{mmol/L}$.
- Lactate >6 .
- pH <7.0 .
- Anion gap >16 .
- Plasma osmolality >350 .
- Plasma $\text{Na}^+ >160$.
- CVA or ACS.
- Significant comorbidities, e.g. cardiac or renal failure.

HHS: management key points

(See Box 9.3.)

Box 9.3 Management key points: HHS (HONK)

- *IV fluid*: may require 8–10L in the first 48h. Start with 1L of normal saline over the first hour, then 1L 2-hourly for 4h, then 1L 6-hourly until rehydrated. Slower rates in frail and elderly. Aim for a rate of fall of Na^+ of $<10\text{mmol/L}$ in 24h. Consider 0.45% saline if plasma osmolality not decreasing despite positive balance.
- *Insulin infusion*: use low-dose IV insulin (0.05U/kg/h) only if ketonaemia (urine $>2+$ or plasma >1) or if blood glucose not falling with rehydration alone.
- Treat the underlying cause (e.g. antibiotics for suspected infection).
- Thromboprophylaxis unless contraindicated.
- Monitor fluid balance (insert urinary catheter; may need CVP line insertion).
- Monitor U&Es, glucose, and plasma osmolality hourly for first 6h, and 2-hourly thereafter if response satisfactory. (Biochemistry can take 72h to normalize.)
- Refer to the diabetes team for specialist input and patient education.

Further reading

Joint British Diabetes Societies Inpatient Care Group (2012). *The management of hyperosmolar hyperglycaemic state (HHS) in adults with diabetes*.  http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_HHS_Adults.pdf

Hypoglycaemia: assessment

- All unconscious patients should be assumed to be hypoglycaemic until proven otherwise. *Always* check a blood glucose using a bedside blood glucose meter immediately, and *confirm* with a lab glucose.
- Almost 8% of adult inpatients experience hypoglycaemia. The most common cause of coma in a patient with DM is hypoglycaemia due to insulin or sulfonylureas.
- Patients who are *not* known to have DM should have laboratory blood glucose, and insulin and C-peptide determination (for insulinoma or factitious drug administration) *before* glucose treatment.

Presentation

Sympathetic overactivity (glucose $<3.6\text{mmol/L}$)

- Tachycardia.
- Palpitations.
- Sweating.
- Anxiety.
- Pallor.
- Tremor.
- Cold extremities.

Neuroglycopenia (glucose $<2.6\text{mmol/L}$)

- Confusion.
- Slurred speech.
- Focal neurological defect (stroke-like syndromes).
- Coma.

- Patients with well-controlled DM have more frequent episodes of hypoglycaemia and can become desensitized to sympathetic activation. These patients may develop neuroglycopenia before sympathetic activation and complain of 'loss of warning' (hypoglycaemic unawareness).
- β -blockers blunt the symptoms of sympathetic activation, and patients taking these drugs lose the early warning of hypoglycaemia.
- Patients with poorly controlled DM develop sympathetic signs early and avoid these by running a high blood glucose. They may complain of having a 'hypo' when their blood sugar is normal or high. They do not require glucose treatment. Re-education and gradual improvement of glucose control may be needed.
- Patients who have type 1 or pancreatic diabetes for a longer duration may have more frequent and severe episodes of hypoglycaemia.

Investigations

- Blood glucose (bedside glucose meter must be confirmed by lab glucose for a new admission or hypoglycaemic coma).
- For patients not known to have DM, take blood (clotted, heparin, and fluoride oxalate tubes) *prior* to giving glucose, for insulin and C-peptide levels (send blood to the lab on ice for immediate centrifugation).
- Other investigations depend on the presentation (new admission vs inpatients) and cause (dictated by history and medications) (see Box 9.4).

Note

- A lab glucose of $<2.2\text{mmol/L}$ is defined as a severe attack.
- Coma usually occurs with blood glucose $<1.5\text{mmol/L}$.
- Low C-peptide and high insulin levels indicate exogenous insulin; high C-peptide and insulin levels indicate endogenous insulin, e.g. surreptitious drug (sulfonylurea) ingestion or insulinoma.

Causes of hypoglycaemia

In the majority of inpatients with DM, hypoglycaemia occurs due to:

- $\uparrow$ insulin and sulfonylureas:
 - Prescription errors such as wrong insulin, dose, or time.
 - Inappropriate use of drugs or insulins.
 - Sliding scale.
- $\downarrow$ insulin or medication requirements:
 - Acute illness, e.g. sepsis, renal or liver failure.
 - Drugs, e.g. reduction in steroids.
 - Reduced oral intake or change in dietary pattern.

Other causes are summarized in Box 9.4 and should be considered in any new presentation or recurrent causes of hypoglycaemia.

Box 9.4 Causes of hypoglycaemia**Drugs**

- Insulin.
- Sulfonylureas.
- Alcohol.
- Salicylates.
- Prescription errors (e.g. chlorpropamide for chlorpromazine).
- Others:
 - Disopyramide.
 - β -blockers.
 - Pentamidine.
 - Quinine.

Organ failure

- Hypopituitarism (especially acute pituitary necrosis).
- Acute liver failure.
- Acute renal failure.
- Adrenal failure.
- Myxoedema.
- Rarely CCF.

Infections

- Sepsis syndrome.
- Malaria.

Tumours

- Insulinoma.
- Insulin growth factor-2 (IGF-2) secreting.

Hypoglycaemia: management

Acute measures

(See Box 9.5.)

- Remember to *take blood* prior to glucose administration (glucose, insulin, C-peptide) (➡ Hypoglycaemia: assessment, pp. 556–7).
- If there is a history of chronic alcohol intake or malnourishment, give IV *thiamine* 1–2mg/kg to avoid precipitating WE.
- Mild* (patient conscious, orientated, and able to swallow):
 - If the patient is conscious and cooperative, give 15–20g of quick-acting carbohydrate (see Box 9.5). Test glucose after 10–15min; if <4mmol/L, repeat treatment up to three times.*
- Moderate* (patient conscious, but confused/disorientated or aggressive, and able to swallow):
 - If cooperative and safe to swallow, treat as for mild hypoglycaemia; otherwise give either 1.5–2 tubes of Glucogel® squeezed into the mouth between the teeth and gums or treat as for severe hypoglycaemia. Test glucose after 10–15min; if <4mmol/L, repeat treatment up to three times.*
- Severe* (patient unconscious, fitting, or aggressive):
 - 80mL of 20% glucose IV over 10min (or 160mL of 10% glucose IV over 10min); 50% glucose IV is not advised.
 - If IV access is difficult, give 1mg of *glucagon* IM. Glucagon is not effective if recurrent hypos, liver disease, starved, or NBM and can only be used once. Test glucose after 10–15min. It should be >4mmol/L.*

Box 9.5 Oral treatment options for hypoglycaemia (15–20g of fast-acting carbohydrate)

- 1.5–2 Glucogel® tubes—can also be used if buccal absorption desired.
- Half a can of Coke™.
- 200mL of orange juice.
- 40mL (to be diluted) of Ribena™ original.
- 4–5 Glucotabs®.
- Four heaped teaspoons of sugar dissolved in water.

* If repeated three times, consider IV 10% glucose at 100mL/h or 1mg glucagon IM (if no IV access and not given already). Once blood glucose >4mmol/L, give 20g of long-acting carbohydrate (two biscuits or a slice of bread) or the next meal if due. If IM glucagon given, give 40g of long-acting carbohydrate to replenish glycogen stores. If NBM, give 10% glucose infusion at 10mL/h and review glucose hourly.

Hypoglycaemia: further management

Further management

- Review glucose regularly in all patients. Give hypoglycaemia education, and refer to the diabetes specialist nurse (DSN) if diabetic.
- Patients should regain consciousness or become coherent within 10min, although complete cognitive/neurological recovery may lag by 30–45min. Do not give further boluses of IV glucose without repeating the blood glucose. If the patient does not wake up after ~10min, repeat the blood glucose and consider another cause of coma (e.g. head injury while hypoglycaemic; ➡ Head injury: presentation, p. 380).
- Prolonged severe hypoglycaemia (>4h) may result in permanent cerebral dysfunction.
- Patients on sulfonylureas may become hypoglycaemic following a CVA or other illness preventing adequate food intake.
- Recurrent hypoglycaemia may herald the onset of diabetic nephropathy, as this decreases insulin requirements—insulin is partly degraded by the kidney and sulfonylureas are really excreted.
- Review the patient's current medication, and inspect all tablets from home.
- Admit if risk of recurrent hypoglycaemia, e.g. with OD of long-acting insulin or sulfonylurea. Observe with hourly blood glucose and 10% IV glucose at 125mL/h.
- Consider psychiatric review if self-inflicted.
- Two episodes of hypoglycaemia requiring emergency (third-party) assistance requires Driver and Vehicle Licensing Authority (DVLA) notification [one episode if category C (heavy goods vehicle, HGV) licence].

For key points in the management of hypoglycaemia, see Box 9.6.

Box 9.6 Management key points: hypoglycaemia

- If the patient can swallow, give 15–20g of fast-acting carbohydrate (see Box 9.5). Check blood glucose again in 10–15min and if still <4, repeat ×3. Follow with a starchy snack. Do not drive for 45min.
- If the patient is unable to swallow, give 80mL of 20% glucose or 160mL of 10% glucose IV. If no IV access: 1mg of glucagon IM. Monitor blood glucose again in 10–15min. Give a carbohydrate-rich snack when the patient is able to eat or IV 10% glucose at 125mL/h.
- Give IV thiamine prior to glucose in alcoholics to reduce the risk of precipitating WE.
- Look for the cause of hypoglycaemia which will dictate further investigations and management.
- Do not omit subsequent regular doses of insulin or medications—but doses may need to be reduced.

Further reading

Joint British Diabetes Societies for Inpatient Care (2018). *The hospital management of hypoglycaemia in adults with diabetes mellitus*, 3rd edn. 🌐 https://diabetes-resources-production.s3.eu-west-1.amazonaws.com/resources-s3/2018-05/JBDS_HypoGuidelineRevised2.pdf%2008.05.18.pdf

Urgent surgery or procedures in patients with diabetes

Surgery and certain procedures require patients to fast for several hours. In addition, general anaesthesia and surgery produce significant stresses on an individual. The hormonal response to stress involves a significant rise in counter-regulatory hormones to insulin, in particular cortisol and adrenaline. For this reason, patients with DM undergoing surgery will still need insulin despite their fasting state.

Current guidelines for elective procedures advise regular glucose monitoring and avoiding variable-rate insulin infusion (sliding scale), wherever possible, with earlier planned procedures. In most cases of urgent surgery or procedures, patients may need insulin infusion as they may be acutely unwell. If >1 missed meal or ketones >3 , variable-rate insulin infusion is needed. Aim for blood glucose of 6–10mmol/L. Give 0.45% saline with 5% glucose and 0.15% or 0.3% KCl as maintenance fluid with the insulin infusion. Continue long-acting analogues, and discontinue insulin infusion after the first meal with short-acting insulin or the usual medications. Surgery in patients with HHS or DKA should be avoided unless life-threatening emergency.

Further reading

Joint British Diabetes Societies for Inpatient Care (2016). *Management of adults with diabetes undergoing surgery and elective procedures: improving standards*, revised March 2016. https://www.diabetes.org.uk/resources-s3/2017-09/Surgical%20guidelines%202015%20-%20full%20FINAL%20amended%20Mar%202016_0.pdf

Diabetic foot complications

While in hospital, 2.2% of patients will develop a diabetic foot complication. A foot problem should be excluded in all patients with DM. All patients admitted with DM should have a thorough foot examination (inspect for any ulceration and deformity, inspect footwear, palpate foot pulses, and test sensation). Complications, including any new ulcer, swelling, discoloration, infection, hot area, blisters, deformity, pain, and cold or pale feet, should be managed with prompt referral to a multidisciplinary footcare team (see Box 9.7).

Box 9.7 Management of diabetic foot problems

- All new diabetic foot problems should be referred to the diabetic footcare team. In the interim:
- Diabetic foot ulcers $\pm$ infection: ensure wound swab and MRSA screen taken; measure dimensions and depth of ulcer using sterile equipment, if possible; closely monitor wounds (photographs helpful); change dressings readily; arrange careful debridement of necrotic tissue; FBC, U&Es, bone profile, liver profile, CRP $\pm$ blood cultures; X-ray $\pm$ MRI; use antibiotics and consider intensive systemic antibiotics for non-healing ulcers with active infections, according to local guidelines. Consider specialist footwear to offload pressure and encourage healing, or consider bed rest/immobilization if not possible. Review the need for vascular assessment.
- Osteomyelitis: FBC, U&Es, bone profile, liver profile, CRP, blood cultures; arrange X-ray $\pm$ MRI and vascular assessment. Review and treat any ulceration. Discuss antimicrobial treatment with a microbiologist.
- Acute Charcot's osteoarthropathy: warm, swollen, tender bone deformity. Arrange X-ray $\pm$ MRI. Treatment with immobilization of the affected joint and offloading to prevent further deformity and ulceration. It can be difficult to distinguish from osteomyelitis, cellulitis, or acute gout clinically. X-rays may be normal in early stages. CRP can be mildly elevated. If in doubt, treat with immobilization, as well as for other differentials, while awaiting MRI and specialist foot team review.
- Acutely ischaemic foot: measure the ankle-brachial pressure index (ABPI) (this can be falsely normal due to calcified blood vessels); arrange US arterial duplex; obtain an urgent vascular review.
- Necrotic ulcer/gangrene: treat as for diabetic foot ulcers with systemic (IV) antibiotics; arrange X-ray to exclude air suggestive of gas gangrene (*Clostridium myonecrosis*), which requires urgent surgical intervention; arrange an urgent vascular surgical review for further assessment $\pm$ debridement.

Further reading

National Institute for Health and Care Excellence (2016). *Diabetic foot problems: prevention and management*. NICE guideline [NG19]. <https://www.nice.org.uk/guidance/NG19>

Hyponatraemia: assessment

Presentation

- Mild hyponatraemia (Na^+ 130–135mmol/L) is common, especially in patients taking thiazide diuretics and is usually asymptomatic. Moderate hyponatraemia (Na^+ 120–129mmol/L) is usually asymptomatic, unless it has developed rapidly.
- Severe hyponatraemia ($\text{Na}^+ < 120\text{mmol/L}$) may be associated with disturbed mental state, restlessness, headache, confusion, irritability, and nausea and vomiting. Severe symptoms, such as seizures, GCS scores < 8 or coma, and cardiorespiratory compromise, prevail as Na^+ acutely ($< 24\text{h}$) drops below 115mmol/L.

History

History should focus on drugs, fluid losses (diarrhoea, frequency, sweating), alcohol misuse, symptoms of cortisol deficiency, and symptoms or history of thyroid, cardiac, lung, liver, or renal disease.

Examination

Examination should focus on careful assessment of volume status and, in particular, should assess whether the patient is hypovolaemic, normovolaemic, or overloaded/oedematous. Patients should therefore have an assessment of their lying and standing BP, HR, JVP or CVP, skin turgor, and the presence of oedema or ascites.

Patients who are hyponatraemic and hypovolaemic are salt-depleted.

Investigations

- In addition to U&Es, other tests should be aimed at excluding other causes of hyponatraemia (➡ Hyponatraemia: causes, pp. 372–3).

Common initial tests include:

- Measurement of serum osmolality and its comparison to the calculated osmolality [$2 \times (\text{Na}^+ + \text{K}^+) + \text{urea} + \text{glucose}$]. An increase in osmolar gap is seen with substances such as ethylene glycol, severe hyperglycaemia, mannitol, etc.
- Spot urine Na^+ estimation, combined with clinical assessment of fluid status, may help determine the underlying cause:
 - Volume depletion from an extrarenal cause (➡ Hyponatraemia: causes, pp. 372–3) is normally associated with a low urinary Na^+ ($< 10\text{mmol/L}$).
 - Volume depletion with a high urinary Na^+ ($> 20\text{mmol/L}$) suggests inappropriate renal salt-wasting (e.g. intrinsic renal disease, hypothyroidism, adrenal insufficiency, diuretics).
 - Fluid overload with a low urinary Na^+ ($< 10\text{mmol/L}$) is seen in conditions such as CCF, cirrhosis, or nephrotic syndrome where there is Na^+ retention in response to poor renal perfusion.
 - Euvolaemia with high urinary Na^+ is seen with SIADH and rarely with severe myxoedema.

General principles

- Assessment of the patient's volume status (neck veins, orthostatic hypotension, cardiac signs of fluid overload, ascites, skin turgor) will help in both diagnosis and subsequent treatment.
- Mild asymptomatic hyponatraemia will usually respond to treatment of the underlying cause, and no specific therapy is necessary.

Correction of hyponatraemia should be gradual to avoid volume overload and/or central pontine myelinolysis. Aim to restore serum Na^+ to $\sim 125\text{mmol/L}$ actively, and allow to rise gradually after that by treating the underlying cause.

- Chronic hyponatraemia ($>48\text{h}$) can be corrected gradually. Significant acute ($<24\text{h}$) hyponatraemia ($>10\text{mmol/L}$ decline in serum Na^+ or $\text{Na}^+ < 120\text{mmol/L}$) and severe symptomatic hyponatraemia require more aggressive correction and monitoring. Seek expert help (see Box 9.8).
- Patients with cirrhosis and ascites and severe hyponatraemia should have diuretics stopped, as diuretics worsen any reduction in tissue perfusion and therefore reduce the ability to excrete free water.
- SIADH or other conditions associated with plasma volume expansion can cause hypouricaemia ($\uparrow$ renal clearance). Urate levels can therefore be useful in differentiating hyponatraemia due to SIADH from other causes of low Na^+ .

Box 9.8 Typical initial investigations for hyponatraemia

- | | |
|---------------------------------------|----------------------|
| ● U&Es. | ● TFT. |
| ● Serum osmolality. | ● 9 a.m. cortisol. |
| ● Urine Na^+ and osmolality. | ● Glucose. |
| ● Igs. | ● Lipid profile. |
| ● Serum electrophoresis. | ● CXR $\pm$ CT head. |

Hyponatraemia: causes

Decreased serum osmolarity

Hypovolaemia (hyponatraemia + hypovolaemia = salt depletion)

Renal losses (urinary Na^+ >20mmol/L)

- Diuretics.
- Addison's disease.
- Na^+ -losing nephropathies.
- Cerebral salt wasting.

Non-renal losses (urinary Na^+ <20mmol/L)

- GI losses (diarrhoea, vomiting).
- Burns.
- Fluid sequestration (e.g. peritonitis, pancreatitis).

Normovolaemia (normal or mildly increased extracellular volume)

SIADH: urine osmolarity >100, serum osmolarity low (<280), urine Na^+ >30mmol/L.

CNS disorders

- Trauma.
- Stroke /SAH.
- Malignancy (primary/secondary).
- Vasculitis (e.g. SLE).
- Infection (abscess or meningoencephalitis).

Malignancy

- Lung (oat cell).
- Pancreas.
- Lymphoma or leukaemia.
- Prostate.
- Urinary tract.
- Head and neck carcinoma.

Pulmonary disease

- Pneumonia.
- TB.
- Lung abscess.
- Cystic fibrosis.
- Lung vasculitis.

Drugs

(via SIADH $\pm$ $\uparrow$ renal sensitivity to ADH or Na^+ > water loss)

- Opiates.
- Haloperidol.
- Amitriptyline.
- Cyclophosphamide.
- Vasopressin.
- Thioridazine.
- Carbamazepine.
- Clofibrate.
- Oxytocin.
- Chlorpropamide.
- Thiazides.
- Vincristine.

Miscellaneous causes

- Severe myxoedema.
- Alcohol misuse.
- Psychogenic polydipsia.

Oedematous states

- CCF.
- Severe renal failure.
- Cirrhosis with ascites.
- Nephrotic syndrome.

Normal serum osmolarity

- Pseudohyponatraemia or 'redistributive hyponatraemia' (e.g. lipaemic serum, paraprotein >10g/dL).
- Intracellular shift of Na^+ (e.g. hyperglycaemia, ethylene glycol).

Hyponatraemia: management

- *Exclude pseudohyponatraemia*: lipaemic serum will be obvious (ask the biochemist). Calculate the osmolar gap to check there are no 'hidden' osmoles (➡ Hyponatraemia: causes, pp. 372–3). Always exclude the possibility of artefactual Na^+ from blood taken proximal to an IVI.
- The correction in Na^+ concentration must not exceed 10mmol/L in the first 24h and 8mmol/L per day thereafter. Rapid correction of hyponatraemia must be avoided, as it can result in osmotic demyelination known as 'cerebral pontine myelinolysis' (see Box 9.9).
- Chronic hyponatraemia can be corrected gradually.
- *Symptomatic hyponatraemia* (e.g. seizures or coma): requires a more aggressive initial correction to increase serum Na^+ concentration (see Box 9.10). Seek expert help early.
- *If volume-deplete (dehydrated)*: start an IVI of normal saline (0.9% = 154mmol/L of Na^+); insert a central venous line if indicated. Monitor fluid output. Catheterize the bladder if there is renal impairment. Watch out for heart failure.
- *If not dehydrated*: for patients with moderate SIADH, restrict fluid intake to 500–1000mL/24h. Seek expert help.
- Remember that giving K^+ can raise plasma Na^+ levels in a hyponatraemic subject. The increase in Na^+ concentration caused by concurrent K^+ administration should be taken into account to avoid over-rapid correction of hyponatraemia. Any K^+ added to the infused solution should be considered as Na^+ in the equation below (see Box 9.10), i.e.: $\text{change in } [\text{Na}^+] = \{\text{fluid } [\text{Na}^+ + \text{fluid } [\text{K}^+]] - \text{serum } [\text{Na}^+]\} / (\text{total body water} + 1)$.

Box 9.9 Clinical manifestations of osmotic demyelination

- May be delayed 2–5 days.
- Often irreversible or only partially reversible.
- Dysarthria.
- Dysphasia.
- Diplopia.
- Paraparesis or quadriparesis.
- Lethargy.
- Loss of consciousness.
- 'Locked-in' syndrome.
- Coma or seizures.

Box 9.10 Management key points: hyponatraemia

- In all cases, cause-specific treatment with cessation of offending medications and/or IV fluids is needed. Do not correct serum Na^+ above 10mmol/L in the first 24h.
- If hypovolaemic: IV 0.9% saline and recheck U&Es.
- If hypervolaemic (CCF, renal failure, or cirrhosis): fluid-restrict.
- SIADH: water restriction (about 500–1000mL/day) and seek specialist review.
- Acute hyponatraemia with $>10\text{mmol/L}$ decline in Na^+ : consider 150mL of hypertonic (3%) saline over 20min.* Recheck serum Na^+ in 4h.
- Hyponatraemia with moderate severe symptoms (nausea and vomiting, confusion, headache): seek expert help. Consider 150mL of hypertonic (3%) saline over 20min.* Aim for serum Na^+ increase of $>5\text{mmol}/24\text{h}$. Recheck serum Na^+ in 1, 6, and 12h.
- Hyponatraemia with severe symptoms (seizures, GCS scores <8 , cardiorespiratory compromise, somnolence): seek expert help and involve the local ITU team. Manage the airway; anticonvulsant if fitting. Use 150mL of hypertonic (3%) saline over 20min.* Check serum Na^+ and repeat 150 mL of hypertonic (3%) saline over 20min.* Repeat up to three times until serum Na^+ increases $>5\text{mmol}/\text{L}$. If Na^+ rise $>5\text{mmol}/\text{L}$, use the smallest volume of 0.9% saline and recheck Na^+ at 6 and 12h. If Na^+ rise $<5\text{mmol}/\text{L}$, use the smallest volume of hypertonic (3%) saline infusion to increase serum Na^+ by $1\text{mmol}/\text{L}/\text{h}$.* Monitor serum Na^+ at least 4-hourly. Stop hypertonic (3%) saline infusion if Na^+ increases $>10\text{mmol}/\text{L}$, serum $\text{Na}^+ >130\text{mmol}/\text{L}$, or symptoms resolve.

* Preferably via a central line in an HDU setting. If hypertonic (3%) saline is not available, discuss alternatives with your pharmacist (e.g. 250mL of hypertonic 1.8% saline).

Further reading

National Institute for Health and Care Excellence CKS (2015). *Hyponatraemia*. <http://cks.nice.org.uk/hyponatraemia>

Spasovski G, Vanholder R, Allolio B, et al.; Hyponatraemia Guideline Development Group. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Eur J Endocrinol* 2014;**170**:G1–47. <http://www.eje-online.org/content/170/3/G1.full>.

Hypernatraemia

Abnormalities in serum Na^+ are usually associated with changes in serum osmolality and extracellular volume (ECV).

Presentation

Symptoms often relate to severe volume depletion: weakness, malaise, fatigue, altered mental status, confusion, delirium, or coma.

Many patients with severe hypernatraemia are seen in intensive care, often with an intracranial catastrophe. The cause or mechanism of hypernatraemia in these patients is unknown.

Causes

- Osmotic diuresis (glycosuria), as seen in HHS.
- Critically ill with intracranial pathology.
- Diarrhoea/protracted vomiting.
- Burns.
- Diabetes insipidus (DI) (particularly when the patient becomes unwell and is unable to keep up with oral fluids).
- Respiratory losses (hot, dry environment).
- Iatrogenic (administration of salt/saline or sodium bicarbonate).
- Mineralocorticoid excess (Conn's, Cushing's).

The way to determine the cause of abnormal serum Na^+ is by:

- Careful assessment of the ECV [evaluation of neck veins, supine and standing BP, any cardiac signs of fluid overload (e.g. S3, oedema), and skin turgor], in association with:
- Measuring serum and urine osmolality. Serum osmolality may be estimated by $[2 \times (\text{Na}^+ + \text{K}^+) + \text{urea} + \text{glucose}]$, but this is inaccurate when there are other osmoles (e.g. ketones, ethanol, methanol, ethylene glycol, renal failure) that contribute.

Serum $\text{Na}^+ > 145 \text{ mmol/L}$ is always associated with hyperosmolality.

Management

- Avoid rapid and extreme changes in serum Na^+ concentration. It is safer to change serum Na^+ cautiously. Aim initially for no more than 10 mmol reduction in 24h.
- If there is hypovolaemia, start fluid replacement. Normal saline (0.9%) contains elemental Na^+ at 154 mmol/L. Use this initially to correct hypovolaemia, if present, then change to 5% glucose to replace water and slowly correct Na^+ concentration.
- If the patient is haemodynamically stable, encourage oral fluids.
- Monitor electrolytes twice daily initially, and more frequently if hypernatraemia is known to be acute ($< 48 \text{ h}$).

Acute hypocalcaemia

Presentation

- Abnormal neurological sensations and neuromuscular excitability.
- Numbness around the mouth and paraesthesiae of the distal limbs.
- Hyper-reflexia.
- Carpopedal spasm.
- Tetanic contractions (may include laryngospasm).
- Focal or generalized seizures. Rarely extrapyramidal signs or papilloedema.
- Hypotension, bradycardia, arrhythmias, and CCF.
- Chvostek's sign is elicited by tapping the facial nerve just anterior to the ear, causing contraction of the facial muscles (seen in 10% of normals).
- Trousseau's sign is elicited by inflating a BP cuff for 3–5min 10–20mmHg above the level of SBP. This causes mild ischaemia and unmasks latent neuromuscular hyperexcitability, and carpal spasm is observed. (Carpopedal spasm may also occur during hyperventilation-induced respiratory alkalosis.)

Investigations

- Plasma Ca^{2+} , PO_4^{3-} , and albumin.
- Corrected Ca^{2+} = measured Ca^{2+} + $[40 - \text{serum albumin (g/L)}] \times 0.02$.
- Plasma Mg^{2+} .
- Vitamin D and ALP.
- U&Es.
- ECG (prolonged QT interval).
- Plasma PTH level.
- Skull X-ray (SXR) (intracranial calcification, especially hypoparathyroidism).

Management

- The aim of *acute* management is to ameliorate the acute manifestations of hypocalcaemia, and not necessarily to return Ca^{2+} to normal.
- For frank tetany, 10mL of 10% calcium gluconate (diluted in 100mL of normal saline or 5% glucose) can be given by slow IV injection over 10min. NB: 10mL of 10% calcium chloride (9mmol) contains ~4-fold more Ca^{2+} than calcium gluconate. Calcium gluconate is preferred, as it causes less tissue necrosis if it extravasates. IV Ca^{2+} should never be given faster than this because of the risk of arrhythmia. This initial treatment with IV calcium gluconate is followed with a slow infusion of calcium gluconate—add 100mL of 10% calcium gluconate to 1L of normal saline or 5% glucose. Start the infusion at 50mL/h, and titrate to maintain serum Ca^{2+} in the low-normal range.
- Post-parathyroidectomy, mild hypocalcaemia normally ensues, requiring observation only. In patients who have parathyroid bone disease, however, 'hungry bones' may cause profound hypocalcaemia shortly after the parathyroids are removed. This may cause severe and prolonged hypocalcaemia which requires prolonged treatment.

- Chronic hypocalcaemia is best managed with oral Ca^{2+} , together with either vitamin D or, if the cause is hypoparathyroidism or an abnormality in vitamin D metabolism, a form of hydroxylated vitamin D such as alfacalcidol or calcitriol.
- If Mg^{2+} deficiency is present, add 20mL (~40mmol) of 50% magnesium sulfate solution to 230mL of normal saline (10g/250mL). Infuse 50mL of this (equivalent to 2g of magnesium sulfate, 8 mmol) over 10min, and at 25mL/h thereafter.

For causes of hypocalcaemia, see Box 9.11. For key points on the management of hypocalcaemia, see Box 9.12.

Box 9.11 Causes of hypocalcaemia

- Vitamin D deficiency.
- Hypoparathyroidism:
 - Post-parathyroid, thyroid, or neck surgery.
 - Primary (autoimmune).
 - Neck irradiation.
- CRF: hyperphosphataemia and reduced renal hydroxylation to active vitamin D.
- Pseudo-hypoparathyroidism (PTH resistance—Albright's hereditary osteodystrophy).
- Developmental agenesis of the parathyroids (di George syndrome).
- Loss of Ca^{2+} from circulation:
 - Extravascular deposition.
 - Acute pancreatitis.
 - Hyperphosphataemia (renal failure, tumour lysis syndrome).
 - Osteoblastic metastases (e.g. prostatic).
- Intravascular binding:
 - Citrate (massive blood transfusion).
 - Foscarnet (anti-CMV drug).
 - Acute respiratory alkalosis.
- Mg^{2+} deficiency (gives PTH resistance or decreases PTH secretion if severe).
- Sepsis.
- Burns.
- Fluoride intoxication.
- Spurious—associated with gadolinium contrast for MRI scans
- Chemotherapy (e.g. cisplatin).

Box 9.12 Management key points: hypocalcaemia

- If symptomatic: 10mL of 10% calcium gluconate (diluted in 100mL of normal saline or 5% glucose) over 10min (with cardiac monitor).
- Follow with a slow infusion: 100mL of 10% calcium gluconate in 1L of normal saline or 5% glucose; start infusion at 50mL/h, and titrate to maintain serum Ca^{2+} in the low-normal range.
- Monitor plasma Ca^{2+} twice daily.
- Correct Mg^{2+} deficiency if present.
- Seek expert help regarding oral Ca^{2+} and vitamin D replacement.

Hypercalcaemia

Definition

- Mild—corrected Ca^{2+} 2.65–3mmol/L.
- Moderate—corrected Ca^{2+} 3.01–3.40mmol/L.
- Severe— >3.4 mmol/L.
- The free (ionic) plasma Ca^{2+} concentration is dependent on both arterial pH (increases with acidaemia due to $\downarrow$ protein binding of ionized Ca^{2+}) and plasma albumin.
- Corrected Ca^{2+} = measured Ca^{2+} + $[40 - \text{serum albumin (g/L)}] \times 0.02$; for example, if measured Ca^{2+} = 2.10mmol/L and albumin = 30g/L, corrected Ca^{2+} = 2.10 = $[(40 - 30) \times 0.02] = 2.30$ mmol/L.
- Most blood gas analysers now measure ionized Ca^{2+} .

For causes of hypercalcaemia, see Box 9.13.

Presentation

- Routine biochemical screen in an asymptomatic patient.
- *General*: symptoms are often non-specific and include depression (30–40%), weakness (30%), tiredness and malaise, itching, keratitis, and corneal calcification.
- *GI*: constipation, anorexia, vague abdominal symptoms (nausea, vomiting), weight loss.
- *Renal*: renal calculi (if long-standing); nephrogenic DI (20%); type 1 renal tubular acidosis; pre-renal failure; chronic hypercalcaemic nephropathy, polyuria, polydipsia, or dehydration.
- *Neuropsychiatric*: anxiety, depression, and cognitive dysfunction; coma or obtundation.
- *Cardiac*: hypertension, cardiac dysrhythmias, short QT interval on ECG.

For investigations of hypercalcaemia, see Box 9.14.

Urgent treatment is required if

- $\text{Ca}^{2+} > 3.4$ mmol/L or if symptomatic, i.e.:
 - Clouding of consciousness or confusion is present.
 - Hypotension.
 - Severe dehydration causing pre-renal failure.

Management

- *Rehydrate* patient with IV 0.9% saline. Aim for about 3–6L/24h, depending on fluid status (CVP), urine output, and cardiac function.
- If the patient does not pass urine for 4h, pass a urinary catheter and a central venous line to monitor CVP.
- Stop medications which may be contributing to hypercalcaemia, i.e. thiazide diuretics.
- *Diuretics*: once the patient is rehydrated, continue 0.9% saline infusion and consider adding *furosemide* with care. Avoid further dehydration, and carefully monitor K^+ and other electrolytes and replace if necessary. The usual dose is 20mg every 4h (i.e. with each litre); however, some patients may need a larger dose to avoid pulmonary oedema. Patients need to have K^+ added to all the bags to avoid hypokalaemia with

Box 9.13 Causes of hypercalcaemia

- Primary (or tertiary) hyperparathyroidism (85% of cases).
- Malignancy:
 - Humoral hypercalcaemia [parathyroid hormone-related peptide (PTHrP)-related].
 - Local osteolytic hypercalcaemia (e.g. myeloma, metastases).
- Hyperthyroidism (present in 15–20% of patients, although usually only gives mild hypercalcaemia and is due to excess osteoclast activity).
- Granulomatous disorders (sarcoidosis). Rarely, patients with sarcoidosis and coexisting vitamin D deficiency may develop severe hypercalcaemia when treated with vitamin D.
- Drug-related:
 - Vitamin D intoxication.
 - Vitamin A intoxication.
 - Theophylline toxicity.
 - 'Milk-alkali' syndrome (antacids).
 - Thiazide diuretics.
 - Lithium (mild, present in 50% patients on long-term lithium, as lithium stimulates the parathyroids).
- Immobilization (Paget's disease).
- Dehydration.
- Chronic liver disease.
- Benign familial hypocalciuric hypercalcaemia.
- Human T-lymphotropic virus (HTLV)-1 infection may present with severe hypercalcaemia.
- Pheochromocytoma [part of multiple endocrine neoplasia (MEN) type 2), acromegaly.
- Adrenal failure.
- Rhabdomyolysis (Ca^{2+} may be high or low).
- Congenital lactase deficiency (rare).

Box 9.14 Investigations for hypercalcaemia

- | | |
|---|---|
| • Plasma Ca^{2+} , PO_4^{3-} , and Mg^{2+} . | • CXR. |
| • U&Es. | • Plasma PTH level. |
| • LFTs, including ALP. | • 24h urinary Ca^{2+} with Ca^{2+} :creatinine ratio measurement. |
| • Albumin. | • TFTs. |
| • Vitamin D. | |
| • Serum and urine electrophoresis. | |

Avoid prolonged use of the tourniquet when taking samples for Ca^{2+} measurement

this protocol. In large doses (in combination with large amounts of 0.9% saline), furosemide can help increase Ca^{2+} excretion, although there is some lack of evidence of the efficacy of this approach. Continue monitoring CVP carefully to prevent either fluid overload or dehydration.

- Monitor electrolytes, especially K^+ and Mg^{2+} which may fall rapidly with rehydration and furosemide. Replace K^+ (20–40mmol/L of saline) and Mg^{2+} (up to 2mmol/L saline) IV.
- If this fails to reduce plasma Ca^{2+} adequately (Ca^{2+} still >2.8 mmol/L), then the following measures should be considered:
 - *Bisphosphonates*: inhibit osteoclast activity, thereby causing a fall in plasma Ca^{2+} . Administer *pamidronate* at 30–60mg IV over 4–6h. (As a general rule, give 30mg over 4h if Ca^{2+} is <3 mmol/L or for all patients with significant renal impairment, 60mg over 8h if Ca^{2+} is 3–4 mmol/L.) Ca^{2+} levels begin to fall after 48h and remain suppressed for up to 14 days. *Zoledronic acid* has a shorter infusion time (15min) and is said to be more effective with a longer duration of action.
- *Salmon calcitonin* 400IU q8h. This has a rapid onset of action (within hours), but its effect lasts only 2–3 days (tachyphylaxis). It may also provoke nausea.
- *Steroids* (prednisolone 30–60mg PO od): most effective in hypercalcaemia due to sarcoidosis, myeloma, or vitamin D intoxication.
- Consider use of the calcimimetic ‘cinacalcet’ if hypercalcaemia is due to primary hyperparathyroidism not amenable to surgical treatment.
- *Familial hypocalciuric hypercalcaemia*: elevated Ca^{2+} , normal 24h urinary Ca^{2+} . This causes few symptoms (mild fatigue or lethargy). PTH may be raised, but the patient does not respond to parathyroidectomy.
- Dialysis may be considered in refractory hypercalcaemia or if large fluid loads are not feasible.

For key points in the management of hypercalcaemia, see Box 9.15.

Box 9.15 Management key points: hypercalcaemia

- Discontinue exacerbating medications.
- IV fluids: 3–6L of normal saline in the first 24h. Monitor fluid balance/CVP.
- Once rehydrated, continue normal saline infusion and consider furosemide 20–40mg every 2–4h. Monitor all electrolytes, especially K^+ , and replace as required. If rehydration fails to correct symptoms or Ca^{2+} still >2.8 mmol/L or known underlying malignancy at the outset, give a bisphosphonate—IV pamidronate 30mg over 4h if Ca^{2+} <3 mmol/L or significant renal impairment, 60mg over 8h if Ca^{2+} >3 mmol/L.
- Consider steroids (prednisolone 40–60mg PO od) if hypercalcaemia is secondary to sarcoidosis, hypervitaminosis D, or myeloma.
- Consider dialysis for refractory hypercalcaemia.

Further reading

National Institute for Health and Care Excellence CKS (2014). *Hypercalcaemia*. <http://cks.nice.org.uk/hypercalcaemia>

Hypophosphataemia

Plasma PO_4^{3-} is normally 0.8–1.4 mmol/L. Hypophosphataemia is common and often unrecognized by clinicians. Most intracellular PO_4^{3-} is present as creatine phosphate or adenine phosphates [e.g. adenosine triphosphate (ATP)], and in RBCs, the predominant species is 2,3-diphosphoglycerate. Hypophosphataemia does not necessarily indicate PO_4^{3-} deficiency; similarly, PO_4^{3-} deficiency may be associated with normal or high plasma PO_4^{3-} concentrations. See Box 9.16 for causes of hypophosphataemia.

Presentation

- Most cases of severe hypophosphataemia occur in very sick patients (often in an ITU). *Occasionally seen in asymptomatic patients.*
- Coincident Mg^{2+} deficiency exacerbates PO_4^{3-} depletion, and vice versa.
- Modest hypophosphataemia has no effect but warrants investigation. Severe hypophosphataemia (<0.4 mmol/L) may cause symptoms and requires treatment.

See Box 9.17 for manifestations of severe hypophosphataemia.

Investigations

- Vitamin D and PTH.
- LFTs.
- Aldosterone.
- ABGs.
- Serum glucose.
- Serum and urine electrophoresis.
- 24h urine PO_4^{3-} .

Treatment

- PO_4^{3-} repletion should generally be reserved for patients with sustained hypophosphataemia (e.g. ≤ 0.4 mmol/L). Treatment of the underlying cause (DKA, diarrhoea, vitamin D deficiency) will often correct hypophosphataemia.
- Orally, give effervescent Phosphate Sandoz® two tablets tds or potassium phosphate IV (9–18 mmol/24h).
- IV PO_4^{3-} replacement can be considered in severe deficiency but should be used with care. Aggressive IV PO_4^{3-} therapy can cause hypocalcaemia with seizures and tetany, as well as renal impairment and potentially arrhythmias. Serum PO_4^{3-} and Ca^{2+} levels should be monitored 6-hourly during PO_4^{3-} infusion.
- Excessive PO_4^{3-} replacement may cause hypocalcaemia and metastatic calcification; monitor Ca^{2+} , PO_4^{3-} , K^+ , and other electrolytes.
- PO_4^{3-} should not be infused with Ca^{2+} , as this will cause Ca^{2+} to precipitate.

For key points on the management of hypophosphataemia, see Box 9.18.

Box 9.16 Causes of hypophosphataemia**Modest (0.4–0.75 mmol/L)**

- Dietary deficiency.
- Vitamin D deficiency.
- Chronic liver disease.
- Hyperparathyroidism (increases PO_4^{3-} excretion).
- ↓ absorption (e.g. PO_4^{3-} binding antacids).
- Hyperaldosteronism.
- Diuretics.
- Fanconi's syndrome (may be secondary to myeloma).

Severe (<0.4 mmol/L)

- Respiratory alkalosis or ventilation.
- Treatment of DKA.
- Alcohol withdrawal.
- Acute liver failure.
- Refeeding syndrome.
- Hungry bones (post-parathyroidectomy).
- Lymphomas or leukaemias.
- Neuroleptic malignant syndrome.
- Raised 'phosphatonins', such as fibroblast growth factor (FGF)-23, which increase PO_4^{3-} excretion.

Box 9.17 Manifestations of severe hypophosphataemia

- Myopathy (involving the skeletal muscle and diaphragm).
- Rhabdomyolysis.
- Cardiomyopathy.
- Erythrocyte dysfunction, including haemolysis.
- Leucocyte dysfunction.
- Metabolic acidosis.
- CNS dysfunction (encephalopathy due to ATP depletion, irritability, seizures, paraesthesiae, coma).
- Respiratory failure.
- Reduced platelet half-life.
- Mineral mobilization.
- Hypercalciuria due to ↓ tubular Ca^{2+} reabsorption.
- Prolonged hypophosphataemia leading to rickets and osteomalacia.

Box 9.18 Management key points: hypophosphataemia

- Treatment of the underlying cause is often sufficient to treat mild hypophosphataemia without initiating replacement therapy.
- Oral supplementation is preferable for mild to moderate deficiency.
- IV PO_4^{3-} supplementation should be used with caution and requires careful monitoring of other electrolytes 6-hourly. Patients should be placed on a cardiac monitor. Peripheral administration can be painful, and extravasation can cause tissue damage.
- Do not infuse with Ca^{2+} salts due to the risk of precipitation.

Addisonian crisis: assessment

Adrenocortical insufficiency may be subclinical for days or months in otherwise well individuals. Stress, such as infection, trauma, or surgery, may precipitate an Addisonian crisis, with cardiovascular collapse and death if the condition is not suspected (see Boxes 9.19 and 9.20). Crises may also occur in patients with known Addison's disease on replacement hydrocortisone if they fail to increase their steroid dose with infections. For causes of adrenal failure, see Box 9.19.

Presentation

- Hypotension and cardiovascular collapse (shock).
- Faintness, particularly on standing (postural hypotension).
- Anorexia, weight loss, nausea, vomiting, and abdominal pain.
- Hyponatraemia and hyperkalaemia.
- Dehydration (thirst may not be apparent because of low Na^+).
- Salt cravings.
- Diarrhoea in 20% of cases.
- Symptoms of precipitant: fever, night sweats (infection), flank pain (haemorrhagic adrenal infarction), etc. Note signs/symptoms of other endocrinopathies.
- Non-specific: weight loss, fatigue, weakness, myalgia, low-grade fever, headache, cramps, joint pain.
- Hyperpigmentation suggests chronic hypoadrenalism.
- Loss of axillary or pubic hair in women.
- Psychiatric features are common and include asthenia, depression, apathy, and confusion (treatment with glucocorticoids reverses most psychiatric features).

Autoimmune adrenalitis

Accounts for 70–90% of cases in developed countries. Look for clinical evidence of other autoimmune disorders.

TB adrenalitis

Worldwide this is the most common cause of adrenal insufficiency.

Adrenal infiltration

Malignant secondaries may be present in the adrenals of a high percentage of patients with lung cancer, breast tumours, and malignant melanomas. Adrenal failure will only occur when over 90% of the gland is replaced by metastases.

The adrenals may alternatively be infiltrated in primary adrenal lymphoma, sarcoidosis, amyloidosis, and haemochromatosis.

Practice points

- Seventy-five per cent of patients with autoimmune adrenalitis have one or more other autoimmune disorders such as polyglandular autoimmune syndrome type 1 or 2.
- Never forget Addison's disease in a sick patient when the diagnosis is unclear.
- Patients with adrenal insufficiency should be informed of sick day rules and should carry a steroid card or a MedicAlert bracelet/pendant.

Box 9.19 Recognized causes of adrenal failure

Common

- Autoimmune adrenalitis (70%).
- TB of the adrenals (10–20%).

Rare

- Malignant secondaries in the adrenal glands.
- Adrenal haemorrhage, including meningococcal septicaemia.
- Disseminated fungal infection (histoplasmosis, paracoccidioidomycosis).
- Hypopituitarism.
- Drugs: metyrapone or aminoglutethimide can precipitate adrenal failure. Other drugs (see Box 9.20) may cause relative adrenal insufficiency.
- Congenital conditions.
- Adrenoleukodystrophy.
- Congenital adrenal hyperplasia.
- Familial glucocorticoid deficiency.
- HIV.
- Bilateral adrenalectomy.

Box 9.20 Causes of relative adrenal insufficiency

- Drugs:
 - Metyrapone or aminoglutethimide.
 - Ketoconazole.
 - Etomidate.
 - Rifampicin, phenytoin, and phenobarbital.
 - Trilostane.
 - Megestrol acetate.
 - Mifepristone.
- HIV.
- Severe sepsis.
- Burns.
- Acute or chronic liver failure.

Adrenal haemorrhage

This may complicate sepsis (meningococcal septicaemia, Waterhouse–Friderichsen syndrome), traumatic shock, coagulopathies, and ischaemic disorders.

- Severe stress substantially increases the arterial blood supply to the adrenals. However, the adrenal gland has only one or two veins, making it vulnerable to venous thrombosis.
- Blood tests: a precipitous drop in Hb, hyponatraemia, hyperkalaemia, acidosis, uraemia, and neutrophilia.
- *Waterhouse–Friderichsen syndrome* is the association of bilateral adrenal haemorrhage with fulminant meningococcaemia. Adrenal haemorrhage can also be seen with other Gram –ve endotoxaemias such as *Diplococcus pneumoniae*, *Haemophilus influenzae* B, and DF-2 bacillus infections.

Hypopituitarism

As there is no mineralocorticoid deficiency (the release of which is renin, not ACTH-dependent), salt and water loss and shock are less profound than in primary Addison's disease.

Drugs

Rifampicin, phenytoin, and phenobarbital accelerate the metabolism of cortisol and may precipitate an Addisonian crisis in partially compromised individuals or in those on a fixed replacement dose. Most adrenal crises precipitated by rifampicin occur within 2 weeks of initiating therapy.

Addisonian crisis: management

Investigations

- **U&Es** Hyponatraemia and hyperkalaemia (rarely $>6.0\text{mmol/L}$). High urea:creatinine ratio, indicative of hypovolaemia.
- **FBC** Anaemia [normal mean corpuscular volume (MCV)], moderate neutropenia with relative eosinophilia/leucocytosis.
- **Glucose** Hypoglycaemia (rarely).
- **Ca^{2+}** May be high.
- **Cortisol** Baseline $<400\text{nmol/L}$. In sick patients, an expected cortisol level is in the range of 1000nmol/L (NB may be difficult to interpret in a patient on oestrogen therapy due to $\uparrow$ binding proteins).
- **ABG** Mild metabolic acidosis, respiratory failure.
- **Urine** MC&S for infection; urinary Na^+ may be high despite hyponatraemia/hypovolaemia.
- **CXR** Previous TB, bronchial carcinoma.
- **AXR** Adrenal calcification.

Management

(See Box 9.21.)

- Treatment may be required before the diagnosis is confirmed.
- General measures include O_2 , continuous ECG monitoring, CVP monitoring, urinary catheter (for fluid balance), and broad-spectrum antibiotics for underlying infection.
- **Treat shock** (➡ Shock: management, pp. 332–3): give IV normal saline for hypotension—1L stat, then depending on response and clinical signs. Inotropic support may be necessary.
- Give IV glucose if hypoglycaemic.
- If an adrenal crisis is suspected, the patient needs glucocorticoids urgently. Take blood for cortisol and ACTH measurement, and then administer glucocorticoid. Use of *dexamethasone* is now generally discouraged. Hydrocortisone should be administered IV (100mg qds initially). Commencing hydrocortisone can do little harm and may be lifesaving. The dose can later be reduced to an oral maintenance regime once the patient has stabilized, which may be up to 72h.
- **Short Synacthen® test** (omit if the patient is known to have Addison's disease): take baseline blood sample (serum) and administer tetracosactide (Synacthen®) 250 micrograms IM or IV. Take further samples at 30 and 60min for cortisol assay.
- **Fludrocortisone** (50–100 micrograms daily PO) in patients with adrenal insufficiency when stabilized on oral replacement doses of hydrocortisone. Mineralocorticoid replacement is not initially required, as large doses of glucocorticoids confer some mineralocorticoid activity.

Prevention

- Patients on long-term steroid therapy and/or known adrenocortical failure should be instructed to increase steroid intake for predictable stresses (e.g. elective surgery, acute illnesses with fever $>38^\circ\text{C}$) or planned excessive exertion.
- For mild illnesses, if not vomiting, double the oral dose. Vomiting requires IV/IM therapy (hydrocortisone 50–100mg qds).

- For minor operations or procedures (e.g. cystoscopy), give hydrocortisone 100mg IV/IM as a single dose before the procedure, then give double the patient's usual oral dose for the next 24h.
- More serious illnesses require hydrocortisone 100mg qds IV/IM until recovered or for at least 72h, at which point the patient should then take double their normal oral dose for at least 48h when doses can be tailed back down to normal.
- Double replacement doses when stabilized if on enzyme-inducing drugs.

See Table 9.3 for equivalent doses of glucocorticoids.

Box 9.21 Management key points: Addisonian crisis

- IV fluids: 1L of normal saline stat, then according to response.
- Treat hypoglycaemia with IV glucose.
- Steroid replacement: IV in the acute situation. Dexamethasone 8mg can be used, as it will not interfere with cortisol assay for Synacthen® testing. However, using hydrocortisone is now much more common. **DO NOT delay steroids:** give 100–200mg IV hydrocortisone stat, followed by 100mg IV qds for 72h, before switching back to oral steroids.
- Maintenance oral dose may need to be higher while the patient continues to recover. Failure to give adequate steroids during recovery is a cause of relapse into an Addisonian crisis.
- Fludrocortisone 50–100 micrograms od when stabilized on oral hydrocortisone replacement (in patients with primary adrenal failure).
- Advise regarding sick day rules: if still able to eat and drink, double the daily dose. If vomiting, needs IM/IV hydrocortisone 50–100mg tds. Provide with IM hydrocortisone supply at home and a MedicAlert bracelet.
- Patients should know to increase the dose of their steroid replacement before planned strenuous activity.

Table 9.3 Equivalent doses of glucocorticoids¹

Drug	Equivalent dose (mg)
Dexamethasone	0.75
Methylprednisolone	4
Triamcinolone	4
Prednisolone	5
Hydrocortisone	20
Cortisone acetate	25

References

1. *British National Formulary* (1995). Section 6.3.2. Pharmaceutical Press, London; p. 615.

Further reading

- National Institute for Health and Care Excellence (2016). *Addison's disease: management*. <https://cks.nice.org.uk/addisons-disease>
- Society for Endocrinology (2015). *Adrenal insufficiency. Patient booklet*. https://www.endocrinology.org/media/1767/16-04_adrenal-insufficiency.pdf

Myxoedema coma

A common precipitant of coma is the use of sedatives, and subsequent hypothermia, in elderly ♀ patients with undiagnosed hypothyroidism.

Myxoedema coma has a high mortality (30–50%) if inadequately treated.

Presentation

- Altered mental status: disorientation, lethargy, frank psychosis.
- Coma (symmetrical, slow-relaxing reflexes; ~25% have seizures).
- Hypothermia.
- Bradycardia, hypotension (rare).
- Hypoventilation.
- Hypoglycaemia.

Investigations

- *U&Es* Hyponatraemia is common (50%).
- *Glucose* Hypoglycaemia may occur.
- *FBC* Normocytic or macrocytic anaemia (there may be coexisting pernicious anaemia).
- *CK* Often elevated due to myositis.
- *TFT* T4 and TSH.
- *Cortisol* There may be coexisting adrenal insufficiency.
- *ABG* Hypoventilation causing respiratory acidosis.
- *Septic screen* Blood and urine cultures—full examination essential, especially in the elderly.
- *CXR* Pericardial effusion may occur, also as part of septic screen.
- *ECG* Small complexes (pericardial effusion), prolonged QT interval. MI can precipitate myxoedema coma in pre-existing disease.

Poor prognostic indicators

- *Hypotension*: patients with hypothyroidism are usually hypertensive due to high compensatory endogenous catecholamines. Reduced BP indicates possible adrenal failure or cardiac disease. Response to inotropes is poor, as patients are usually maximally vasoconstricted.
- *Bradycardia*.
- *Hypothermia unresponsive to treatment*.
- *Sepsis*.
- *Reduced GCS scores and use of sedative medications*.
- *Hypoventilation and need for mechanical ventilation*: is the most common cause of death in patients with myxoedema coma. The hypoxia responds poorly to O₂ therapy which tends to exacerbate hypercapnia.

Management

(See Box 9.22.)

- Transfer the patient to ICU and monitor closely.
- Mechanical ventilation should be instituted for respiratory failure.
- CVP line: patients may be hypertensive and hypovolaemic, as chronic myxoedema is compensated for by rising catecholamines.

- Hydrocortisone (100mg IV 6- to 8-hourly) until adrenal insufficiency is excluded.
- Institute thyroid hormone replacement therapy before confirming the diagnosis. No consensus has been reached about optimal thyroid hormone replacement. An accepted regimen includes administration of a loading dose of IV thyroxine (T4) 300–500 micrograms (depending on the patient's age, weight, and risk of IHD), followed by daily IV doses of 50–100 micrograms until the patient can take oral T4. If there is no improvement within 24–48h, IV tri-iodothyronine (T3) (10 micrograms 8-hourly) is added and continued until there is clinical improvement and the patient is stable.
- Broad-spectrum antibiotics should be given, since bacterial infection is a common precipitant of myxoedema coma.
- Correct hypoglycaemia.
- Hypothermia should be corrected gently. A space blanket is usually sufficient. Rapid external warming can cause inappropriate vasodilatation and cardiovascular collapse.

Precipitants of myxoedema coma

- Drugs, including sedatives and tranquillizers.
- Infection.
- Stroke and MI.
- Trauma.

Box 9.22 Management key points: myxoedema coma

- Monitor closely in ITU. Mechanical ventilation should be instituted for respiratory failure.
- IV hydrocortisone: 100mg 6- to 8-hourly until adrenal insufficiency is excluded.
- IV T4: initial dose of 300–500 micrograms, followed by daily IV doses of 50–100 micrograms until the patient can take oral T4. If there is no improvement within 24–48h, add IV T3 (10 micrograms 8-hourly).
- Broad-spectrum antibiotics.
- Appropriate fluid (and glucose) replacement.
- Gentle correction of hypothermia (using a space blanket).

Thyrotoxic crisis: assessment

The term thyrotoxic crisis refers to a constellation of symptoms and signs which together imply a poor prognosis. TFTs provide no discrimination between simple thyrotoxicosis and a thyrotoxic crisis (see Table 9.4). If the diagnosis has not been made, look for clues such as a goitre or exophthalmic Graves' disease. The presentation may be confused with sepsis or malignant hyperthermia. A thyrotoxic crisis carries a mortality rate of 30–50%.

Presentation

Cardiovascular symptoms

- Palpitations.
- Tachycardia/tachyarrhythmias.
- Cardiac failure/oedema.
- Hypotension.
- Arrhythmia.
- Cardiovascular collapse.

CNS symptoms

- Anxiety/agitation.
- Violent outbursts.
- Psychosis/delirium.
- Fitting/coma.

GI symptoms

- Diarrhoea.
- Vomiting.
- Jaundice.
- Abdominal pain.

General symptoms

- Fever.
- Hyperventilation.
- Sweating.
- Polyuria.

Rarely, patients may present with an apathetic thyroid storm and lapse into a coma, with few other signs of thyrotoxicosis.

Precipitants of thyrotoxic crisis

- Thyroid surgery/general surgery.
- Withdrawal of antithyroid drug therapy/radioiodine therapy.
- Thyroid palpation.
- Iodinated contrast dyes.
- Infection.
- CVA/PE/MI.
- Parturition.
- DKA.
- Trauma or emotional stress.
- Burns.

Investigations

- TFTs (most labs can perform an urgent TSH/free T4 if needed).
- U&Es (? dehydration).
- Ca^{2+} (may be elevated).
- Glucose (may be low).
- FBC (may see raised WBC).
- LFTs (? jaundice, raised ALP).
- Blood and urine cultures.
- CXR (? pulmonary oedema or evidence of infection).
- ECG (rate ? AF).

Table 9.4 Assessment of severity of a thyrotoxic crisis

Temperature (°C) Score	Pulse (bpm)	Cardiac failure	CNS effects	GI symptoms	
Apyrexial	<99	Absent	Normal	Normal	0
>37.2	>99	Ankle oedema	–	–	5
>37.8	>110	Basal crepitations	Agitation	Diarrhoea, vomiting	10
>38.3	>120	Pulmonary oedema	–	–	15
>38.9	>130		Delirium	Unexplained jaundice	20
>39.4	>140		–	–	25
>40			Coma, seizure	–	30

Add the scores for each column.

Add an extra 10 points if AF is present.

Add 10 points if there is a definable precipitant.

A total score of over 45 indicates a thyroid crisis; a score of 25–44 indicates an impending crisis.

Thyrotoxic crisis: management

Patients with a thyrotoxic crisis or impending crisis

(See Box 9.23.)

- Admit the patient to ICU.
- *Fluid balance*: CVP monitoring is essential to avoid precipitating or worsening cardiac failure. In patients with arrhythmias, the CVP will not accurately reflect left-sided pressures and PA pressure monitoring should be considered. GI and insensible (pyrexia and excessive sweating) fluid losses may exceed 5L/day and must be replaced.
- Fever should be treated with *paracetamol* and aggressive *peripheral cooling techniques*. Dantrolene has been occasionally used to control hyperthermia in a thyrotoxic crisis. Do not use salicylates which will displace T4 from thyroxine-binding globulin (TBG) and can hence worsen the storm.
- β -block the patient with propranolol 60–80mg q4h PO or 1mg IV (repeated every 10min as necessary), with cardiac monitoring. Propranolol also inhibits peripheral T4 to T3 conversion. Fever, tachycardia, and tremor should respond immediately. An alternative is esmolol (15–30mg as a bolus, followed by 3–6mg/min infusion).
- If β -blockade is contraindicated (e.g. asthma), consider a calcium channel blocker such as diltiazem.
- *Treat precipitating factors* such as infection (e.g. cefuroxime 750mg IV tds).
- High-dose *antithyroid drugs*: propylthiouracil (PTU) (600mg loading dose, then 200–300mg q4h PO/NG) is more effective than carbimazole (20mg 4-hourly), as it inhibits peripheral T4 to T3 conversion.
- Consider bile acid sequestrants, e.g. colestyramine 2g qds, which can increase faecal excretion of T4.
- *Hydrocortisone*: 100mg 6-hourly. This also inhibits conversion of T4 to T3.
- Enoxaparin 20mg/day SC should be given to very sick patients at risk of thromboembolism.
- Once organification of iodine has been blocked by antithyroid drugs, iodine can be used to inhibit T4 release from the thyroid gland (Wolff–Chaikoff effect). *Lugol's iodine* contains 5% iodine and 10% potassium iodide in water. Give 1mL PO every 6h. *Do not give Lugol's iodine until at least 1h after the antithyroid drugs have been given.* Any iodine given prior to antithyroid medication may increase thyroid hormone stores. Continue iodine-containing preparations for a maximum of 2 weeks (lithium 300mg 8-hourly is an alternative to iodine in allergic patients).
- *Monitor glucose levels* 4-hourly and administer glucose 5–10% as required. Hepatic glycogen stores are readily depleted during a thyroid storm.
- Consider plasmapheresis if refractory to treatment.

Continuing treatment

- Response to treatment is gauged clinically and by serum T3 levels.
- Stop iodine/potassium iodide/lithium and β -blockers when controlled.
- Consider definitive treatment (e.g. surgery or radioactive iodine).
- Treat AF in the usual way (➡ Atrial fibrillation: assessment, pp. 76–7). Higher doses of digoxin may be required, as its metabolism is $\uparrow$. Amiodarone inhibits peripheral T4 to T3 conversion.

Box 9.23 Management key points: thyrotoxic crisis

- Monitored closely in HDU/ICU.
- IV fluids.
- Paracetamol, peripheral cooling techniques.
- Antiarrhythmic drugs.
- PTU 600mg loading dose, then 200mg 4-hourly PO/NG.
- *Propranolol* 60–80mg 4-hourly PO (or 1mg IV, repeated every 10min as necessary). Caution should be taken with complicating cardiac failure.
- *Hydrocortisone* 100mg IV qds (inhibits peripheral T4 to T3 conversion).
- *Lugol's iodine* 1mL qds at least 1h after the first dose of PTU (to block thyroid hormone synthesis first before blocking thyroid hormone release) for a maximum of 14 days (followed by definitive treatment).
- Treat precipitating factors such as infection.
- Thromboprophylaxis.
- Monitor blood glucose.

Further reading

- American Thyroid Association. *Hyperthyroidism (overactive)*. 🌐 <https://www.thyroid.org/hyperthyroidism>
- Carroll R, Matfin G. Endocrine and metabolic emergencies: thyroid storm. *Ther Adv Endocrinol Metab* 2010;1:139–45.

Pituitary apoplexy

Presentation

Pituitary infarction may be *silent* ('*subclinical pituitary apoplexy*'). Apoplexy implies the presence of symptoms. The clinical manifestations may be due to leakage of blood/necrotic tissue into the subarachnoid space or rapid expansion of a suprasellar mass and pressure on local structures. This may be the presenting symptom of the pituitary tumour (see Box 9.24).

- Headache occurs in 95% of cases (sudden onset; variable intensity).
- Visual disturbance occurs in 70%, (usually bitemporal hemianopia).
- ↓ level of consciousness.
- Ocular palsy (up to 70%) causing diplopia, unilateral or bilateral.
- Nausea/vomiting.
- Meningism (common).
- Hemiparesis or rarely seizures.
- Fever, anosmia, CSF rhinorrhoea, and hypothalamic dysfunction (disturbed sympathetic autoregulation with abnormal BP control, respiration, and cardiac rhythm) are all described but are rare.
- Altered mental state, lethargy, delirium, or coma.
- Symptoms of a preceding pituitary tumour.
- Acute hypopituitarism.

Clinically, pituitary apoplexy may be very difficult to distinguish from an SAH, bacterial meningitis, midbrain infarction (basilar artery occlusion), or cavernous sinus thrombosis. Transient neurological symptoms are common in the preceding few days.

The clinical course is variable. Headache and mild visual disturbance may develop slowly and persist for several weeks. In its most fulminant form, apoplexy may cause blindness, haemodynamic instability, coma, and death. Residual endocrine disturbance (panhypopituitarism) invariably occurs.

Investigations

- *U&Es*: hyper- or hyponatraemia may occur.
- *Renal function, LFTs, clotting, and FBC*.
- *Endocrine function tests (save clotted blood)*: cortisol, TFTs, prolactin, growth hormone (GH), IGF-1, luteinizing hormone (LH), follicle-stimulating hormone (FSH). The short Synacthen® test is unreliable in the first 2–3 weeks.
- *CT head*: pituitary cuts with IV contrast will reveal a tumour mass or haemorrhage 24–48h after onset; however, CT is diagnostic in only ~30% of patients.
- *MRI (gadolinium-enhanced with pituitary views)*: is the investigation of choice, and urgent MRI is warranted. May be more informative in the subacute setting.
- *Formal visual field assessment*: preferably in the first 24h if the patient is stable.

Management

(See Box 9.25.)

- Stabilize the patient (airway, breathing, circulation).
- Hydrocortisone 100mg IV should be given if the diagnosis is suspected, *after* the blood samples above have been collected, and is particularly

important in patients with haemodynamic instability. Acute secondary adrenal insufficiency is a major cause of mortality.

- Monitor U&Es and urine output for evidence of DI.
- Patients with macroprolactinomas may respond to dopamine agonists.
- *Neurosurgical decompression* may be indicated (seek neurosurgical review). Obtundation and visual deterioration are absolute indications for neurosurgery. Ideally patients will be nursed on a neurosurgical HDU. Patients without confusion or visual disturbance generally do well without surgery.
- Assess pituitary function once the acute illness has resolved, and treat as necessary. A TSH level in the normal range may be inappropriate if T4 level is low in pituitary disease, but this may occur in the sick euthyroid state, characteristic of many seriously ill patients.

A scoring system has been suggested by the Society for Endocrinology for the assessment of severity of apoplexy, which could serve as a tool for monitoring of conservatively managed patients (see Table 9.5). This system could also be used as an aid to auditing outcomes in surgically and conservatively managed patients.

Table 9.5 Proposed pituitary apoplexy score **

Variable	Points
<i>Level of consciousness</i>	
GCS score 15	0
GCS score <8–14	2
GCS score <8	4
<i>Visual acuity</i>	
Normal* 6/6	0
Reduced—unilateral	1
Bilateral	2
<i>Visual field defects</i>	
Normal	0
Unilateral	1
Bilateral	2
<i>Ocular paresis</i>	
Absent	0
Present—unilateral	1
Bilateral	2

* No change from premorbid visual acuity.

** Reproduced from Rajasekaran S, et al. 'UK guidelines for the management of pituitary apoplexy'. *Clinical Endocrinology*, 2011; **74**(1): 920, with permission from John Wiley and Sons.

Box 9.24 Causes of apoplexy in patients with pituitary adenomas

- Spontaneous haemorrhage (no obvious precipitant, the most common).
- Anticoagulant therapy.
- Head trauma.
- Radiation therapy.
- Drugs (e.g. bromocriptine or oestrogen).
- Following dynamic tests of pituitary function.

Box 9.25 Management key points: pituitary apoplexy

- Have a background suspicion for pituitary apoplexy in patients presenting with acute headache.
- MRI is the investigation of choice, but if contraindicated, a dedicated pituitary CT scan can be performed.
- Hydrocortisone replacement is an important part of management.
- Reduced GCS score and visual deterioration are indications for neurosurgery.
- Full assessment of residual pituitary function is necessary as the patient recovers.

Further reading

Rajasekaran S, Vanderpump M, Baldeweg S, et al. UK guidelines for the management of pituitary apoplexy. *Clin Endocrinol (Oxf)* 2011;**74**:9–20.

Hypopituitary coma

Hypopituitarism does not become evident until 75% of the adenohypophysis is destroyed, and at least 90% destruction is required for total loss of pituitary secretion. Complete loss of hormone secretion can rapidly become life-threatening and requires immediate therapy. In a mild or incomplete form, hypopituitarism can remain unsuspected for years.

Presentation

In the absence of stress, patients with severe hypopituitarism may have few symptoms or signs.

The development of pituitary hormone deficiency tends to follow a characteristic pattern, with GH and gonadotrophins lost early, followed by ACTH and TSH at a later stage. Symptoms of prolactin deficiency are rarely seen, except in the failure of lactation in Sheehan's syndrome.

A general anaesthetic or infection may precipitate hypoglycaemia and coma, due to the combination of a lack of GH, cortisol, and T4, all of which have a counter-regulatory effect on insulin. See Box 9.26 for causes of panhypopituitarism.

Clues from the history include:

- Known pituitary adenoma.
- Recent difficult delivery: pituitary infarction following postpartum haemorrhage and vascular collapse is a recognized cause of hypopituitarism. Features include failure of lactation (deficiency of prolactin and oxytocin), failure of menstruation (lack of gonadotrophins), non-specific features, e.g. tiredness, weakness, loss of body hair, and loss of libido (due to ACTH deficiency, hypothyroidism, and gonadotrophin deficiency).
- Men may give a history of impotence, lethargy, and loss of body hair.
- Women report loss of menstruation.

Examination

- Examination of the comatose patient is discussed under  Coma: assessment, pp. 348–9.
- Examine specifically for secondary sexual characteristics and physical signs of myxoedema.
- Consider other causes for coma ( Coma: assessment, pp. 348–9).

Investigations

- General investigations for patients in coma are discussed under  Coma: assessment, pp. 348–9.
- Take blood for baseline cortisol (9 a.m.), ACTH, TFTs, LH, FSH, prolactin, and GH.
- Short Synacthen® test can be performed to test for adrenocortical reserve ( Addisonian crisis: management, pp. 582–3); however, a test of ACTH reserve, such as the insulin tolerance test or glucagon stress test, may be performed at a later date when the patient has stabilized.
- Luteinizing hormone-releasing hormone (LHRH) and thyrotropin-releasing hormone (TRH) tests may be performed at the same time as the short Synacthen® test but are rarely necessary.

- Defer formal pituitary function testing until the patient is stable.
- CT scan of the pituitary (tumour or empty sella).
- MRI scan may give additional information.

Management

- General measures are as for any patient in coma (➡ Coma: assessment, pp. 348–9).
- Give IV normal saline to restore BP if the patient is in shock.
- Give glucose if the patient is hypoglycaemic.
- Hydrocortisone 100mg IV should be administered if the diagnosis is suspected and continued (100mg IV tds–qds).
- Start liothyronine (10 micrograms bd) *after* hydrocortisone is started.
- Investigate and treat any precipitating intercurrent infection.
- If the patient fails to improve, consider other causes for coma (➡ Coma: assessment, pp. 348–9).
- Long term, the patient will require replacement with hydrocortisone, thyroxine, testosterone or oestrogen/progesterone, and GH.

Box 9.26 Causes of panhypopituitarism

Pituitary

- Mass lesion (adenoma, cyst).
- Pituitary surgery or irradiation.
- Infiltration (sarcoid, haemochromatosis).
- Infarction (Sheehan's).
- Apoplexy (haemorrhage).
- Empty sella syndrome (<10% actually have manifest hypopituitarism).
- Trauma, e.g. fractured skull base.
- Infection, e.g. pituitary abscess.

Hypothalamic

- Mass lesion (metastases, e.g. breast, lung; craniopharyngioma, meningioma).
- Radiotherapy.
- Infiltration (sarcoid, histiocytosis).
- Infection (TB).

Phaeochromocytomas: assessment

- Phaeochromocytomas are catecholamine-producing tumours usually involving one or both adrenal glands. Bilateral tumours are more likely to represent part of a familial syndrome, and tumour location, as well as risk of malignancy, varies depending on the genetic defect. Therefore, the previously described 'rule of 10' for phaeochromocytoma is no longer applicable. Phaeochromocytomas usually secrete adrenaline (AD) or noradrenaline (NA). A small proportion secrete dopamine (DA), when hypotension may occur.
- Most are diagnosed during routine screening of hypertensive patients (they are found in only 0.1% of hypertensives). Pure AD-producing tumours may mimic septic shock due to AD-induced peripheral vasodilatation (β_2 -receptors).

Presentation

- Classically a triad of episodic headaches, sweating, and tachycardia.
- Hypertension (mild to severe sustained or uncontrolled paroxysmal hypertensive episodes) and orthostatic hypotension (low plasma volume); 50% have sustained elevated BP and 50% have paroxysmal elevations.
- Anxiety attacks, tremor, palpitations, cold extremities, and pallor.
- Cardiac dysrhythmias (including AF and VF) and dilated cardiomyopathy.
- Hypertensive crises may be precipitated by β -blockers, tricyclic antidepressants, metoclopramide, and naloxone.
- Unexplained lactic acidosis.
- Triggers for hypertensive crises include surgery (particularly manipulation of the tumour itself), opiates, and contrast media.

See Box 9.27 for other causes of sympathetic overactivity.

Investigations

(See Box 9.28.)

- Two to three 24h urine collections for measurement of metanephrines. These are more sensitive and specific than catecholamines, and false-negative results are rare. Measurements of 24h urine catecholamines remain useful and should be collected if metanephrine measurement is unavailable.
- Urine should be collected in acid-containing bottles and kept refrigerated, as catecholamines are more stable at low pH and low temperature. Urine for metanephrines is collected in the same way.
- Urinary creatinine and volume should be measured to verify an adequate (i.e. 24h) collection.
- In patients who are at high risk for phaeochromocytoma (i.e. familial syndromes or previously surgically cured phaeochromocytoma or paraganglioma), both urine and plasma free metanephrine and normetanephrine should be measured if available (higher sensitivity—~99%).
- Certain drugs (e.g. tricyclic antidepressants, levodopa, prochlorperazine, and calcium channel blockers) should be tapered and discontinued at least 2 weeks before any biochemical tests.

- Catecholamine secretion may be appropriately $\uparrow$ in stress or illness [e.g. stroke, MI, CCF, obstructive sleep apnoea (OSA), and head injury].
- FBC, U&Es, and glucose.
- ECG (may see arrhythmias).
- CXR: roughly 10% of phaeochromocytomas are malignant/metastatic.
- Echocardiogram to assess LV function: this may very rarely identify a mediastinal paraganglioma as the source of catecholamines.
- If the biochemical results are abnormal, imaging with CT or MRI of the abdomen/pelvis is required to locate the tumour. Caution: radiocontrast can cause catecholamine release.
- 123-I-meta-iodobenzylguanidine (MIBG) is taken up by adrenergic tissue. An MIBG scan can detect metastases, multiple lesions, or tumours not detected by CT or MRI.
- *Plasma metanephrines*: are highly sensitive and specific. They should be taken from a patient after at least 15min in a recumbent position. If plasma metanephrines are unavailable, *plasma catecholamines* should be collected from an indwelling cannula placed over 30min previously in a supine patient. Samples need to be taken directly to the lab (on ice) for centrifugation.
- *Selective venous sampling* may be used to localize extra-adrenal tumours.

Box 9.27 Other causes of sympathetic overactivity

- Abrupt withdrawal of clonidine or β -blockers.
- Autonomic dysfunction, e.g. GBS or post-spinal cord injury.
- Stress response to surgery, pain, panic, or acute illness.
- Sympathomimetic drugs:
 - Phenylpropanolamine (decongestant).
 - Cocaine.
 - MAOI plus tyramine-containing foods (cheese, beer, wine, avocado, bananas, smoked or aged fish/meat).

Box 9.28 Investigations for suspected phaeochromocytoma

- U&Es ($\downarrow$ K^+ , $\uparrow$ urea).
- Glucose ($\uparrow$).
- At least 2 $\times$ urinary fractionated metanephrines or catecholamines.
- Plasma metanephrines or catecholamines in high-risk patients.
- CT scan or MRI of adrenals.
- MIBG scan.

Phaeochromocytomas: management

Patients are usually volume-depleted at presentation and should be rehydrated prior to initiation of β -blockade; otherwise severe hypotension may occur. β -blockade alone may precipitate a hypertensive crisis and must never be given prior to adequate α -blockade. Labetalol is predominantly a β -blocker and should not be used alone. Long-acting α -blockers prevent escape episodes.

- Adequate fluid replacement with CVP monitoring.
- Acute hypertensive crises should be controlled with *phentolamine* (0.5–1mg IV bolus, repeated as necessary every 15–30min). Alternatively, start an infusion of nitroprusside (0.5–1.5 micrograms/kg/min; typical dose 100 micrograms/min).
- Preparation for surgery:
 - Initiate oral α -blockade: *phenoxybenzamine* 10mg bd, increasing gradually to 20–30mg bd. Higher doses may be required. Monitor BP closely. Tumour β -stimulation may produce excessive vasodilatation and hypotension, requiring inotropic support. Recent studies have shown that prazosin or doxazosin are equally effective and are being used increasingly. α -blockade is necessary for several weeks prior to surgery to allow for adequate circulating volume expansion.
 - When the BP is controlled with phenoxybenzamine, add propranolol 10–20mg tds.
 - Invasive monitoring [PA (Swan–Ganz) catheter and arterial line] is mandatory.
- Hypotension commonly occurs intraoperatively when the tumour is removed, and this should be managed with blood, plasma expanders, and inotropes, as required. Inotropes should only be used when the patient is appropriately fluid-replete. Expansion of intravascular volume 12h before surgery significantly reduces the frequency and severity of post-operative hypotension. Angiotensin II should be available as an alternative inotrope for cases of resistant hypotension.

For key points on the management of phaeochromocytomas, see Box 9.29.

Box 9.29 Management key points: phaeochromocytoma

- Urine metanephrines are preferable to urine catecholamines if available.
- Ensure the patient is fluid-replete prior to commencing α -blockade.
- Careful preoperative preparation is essential to avoid an intraoperative crisis. PO phenoxybenzamine is now commonly used for this purpose, and patients tolerate anaesthesia well under this protocol.²
- All phaeochromocytoma surgery should be carried out by experienced surgeons and anaesthetists in a specialist centre.
- Have a low threshold for considering familial phaeochromocytoma/paraganglioma syndromes (see Box 9.30), and refer/test appropriately.

Box 9.30 Autosomal dominant endocrine syndromes at high risk of developing phaeochromocytoma

- Consider genetic testing if:
 - Young age at presentation.
 - Family history.
 - Bilateral or multifocal disease.
 - Malignant disease.
 - Other symptoms or signs of endocrine syndrome.
- *Neurofibromatosis (von Recklinghausen disease)*: neurofibromata, café-au-lait spots, Lisch nodules (iris hamartomas), and axillary freckling.
- *von Hippel–Lindau disease*: cerebellar haemangioblastomas, retinal haemangiomas, and other neoplasms, including hypernephroma.
- *MEN types 2a* (hyperparathyroidism and medullary thyroid carcinoma) *and 2b* (medullary thyroid carcinoma, bowel ganglioneuromatosis, hypertrophied corneal nerves, marfanoid habitus).
- *Succinate dehydrogenase subunit B and D (SDHB and SDHD) mutations* are known to cause familial paraganglioma syndromes.

References

2. Society for Endocrinology (2010). *Protocol using oral phenoxybenzamine to prepare patients with catecholamine-secreting phaeochromocytoma and paraganglioma for surgery*. https://www.endocrinology.org/media/1780/10-10_protocol_using_oral_phenoxybenzamine.pdf

Further reading

Endobible. *Phaeochromocytoma*. <http://www.endobible.com/condition/phaeochromocytoma/>

Polyuria

Definition: >3L of urine per day.

Presentation

- Confusion (hyponatraemia or dehydration).
- Coma.
- Proteinuria on screening.
- Depression or other psychiatric manifestations.
- Renal stones.

Causes

- Excessive fluid intake.
- Endocrine dysfunction (DM, DI, hypercalcaemia, hyperthyroidism).
- Hypokalaemia.
- Intrinsic renal disease (polycystic kidneys, analgesic nephropathy, medullary cystic disease, amyloidosis) or renal recovery from ATN.
- Post-obstructive uropathy, e.g. after catheterization of a patient in chronic retention.
- Post-renal artery angioplasty.
- Drugs (furosemide, alcohol, lithium, amphotericin B, vinblastine, demeclocycline, cisplatin).

History

- Duration and severity (nocturia, frequency, water consumption at night).
- Family history of DM, polycystic kidneys, and renal calculi.
- Drug history (see ➡ Causes, p. 600).
- Renal calculi (hypercalcaemia).
- Weakness (low K^+), depression (hypercalcaemia).
- Psychiatric history (psychogenic polydipsia; medications, i.e. lithium).
- Endocrine history (menses, sexual function, lactation, pubic hair).
- Other significant pathology (e.g. causes of amyloid).

Investigations

- U&Es (renal disease, hypokalaemia).
- TFTs.
- Glucose (undiagnosed DM).
- Ca^{2+} , PO_4^{3-} , and ALP.
- Plasma and urine osmolality: a urine:plasma osmolality of <1.0 indicates DI, intrinsic renal disease (including low K^+), or hysterical drinking.
- AXR (nephrocalcinosis).
- Lithium levels, if appropriate.
- Dipstick protein and quantification, if indicated.

Management

- Assess fluid status (JVP, BP, postural drop, weight charts, CVP).
- Strict fluid balance and daily weights.
- CVP line may be necessary.
- Measure urinary Na^+ and K^+ (random spot samples will give an indication of the loss of Na^+ or K^+ initially, and if losses are great, accurate timed samples of $<6h$ are possible).

- Urine osmolality (if $>750\text{mOsm/kg}$, there is no abnormality in urine concentrating ability).
- Replace fluid losses, as appropriate, to maintain normal homeostasis, using combinations of saline and glucose.
- Monitor K^+ , Ca^{2+} , PO_4^{3-} , and Mg^{2+} daily or twice daily if necessary.
- If lithium toxicity is present, see  Lithium, pp. 762–3.
- Avoid chasing fluids. At some point, a clinical judgement has to be made to stop replacing urinary losses with IV fluids, to allow the patient reach their 'normal equilibrium'. Once the patient is optimally hydrated and is able to drink freely, then avoid replacing fluids IV to allow physiological homeostasis to occur.
- If DI is suspected, arrange a water deprivation test (see Box 9.31). If anterior pituitary hormones are abnormal, do not perform a water deprivation test, as both cortisol and thyroid deficiency impair excretion of free water.

Box 9.31 Water deprivation test

- Stop all drugs the day before the test; no smoking or caffeine.
- Supervise the patient carefully to prevent surreptitious drinking.
- Empty the bladder after a light breakfast. No further fluids PO.
- Weigh the patient at times 0, 4, 5, 6, 7, and 8h into the test (stop the test if $>3\%$ of body weight is lost).
- Measure serum osmolality and plasma Na^+ at 30min, 4h, and hourly until the end of the test (check that the plasma osmolality rises to $>290\text{mOsm/kg}$ to confirm an adequate stimulus for ADH release).
- Collect urine hourly, and measure the volume and osmolality (the volume should decrease and the osmolality rise; stop the test if urine osmolality $>800\text{mOsm/kg}$, as DI is excluded).
- If polyuria continues, give desmopressin 20 micrograms intranasally at 8h.
- Allow fluids PO (water) after 8h. Continue to measure urine osmolality hourly for a further 4h.

Interpretation

- *Normal response*: urine osmolality rises to $>750\text{mOsm/kg}$ with a small rise after desmopressin.
- *Cranial DI*: urine osmolality remains low ($<400\text{mOsm/kg}$) and increases by $>50\%$ after desmopressin.
- *Nephrogenic DI*: urine osmolality remains low ($<400\text{mOsm/kg}$) and only rises a little ($<45\%$) with desmopressin.
- *Primary (psychogenic) polydipsia*: urine osmolality rises ($>400\text{mOsm/kg}$) but is typically less than the normal response—often difficult to diagnose.

Malignant hyperthermia

Malignant hyperthermia is a drug- or stress-induced catabolic syndrome characterized by excessive muscular contractions, a sudden rise in body temperature, and cardiovascular collapse. It is often related to the use of anaesthetic agents. The incidence is 1:15 000, with a mortality which has significantly reduced from 80% down to <10% due to better treatment and ↑ awareness of the condition. The cause is unknown but may involve abnormal Ca^{2+} homeostasis in skeletal muscle cells. The condition seems to be inherited in an autosomal dominant manner, with variable penetrance. Early recognition of the condition is essential for treatment and survival.

See Box 9.32 for drugs precipitating malignant hyperthermia. See Box 9.33 for drugs considered safe in malignant hyperthermia.

Box 9.32 Drugs precipitating malignant hyperthermia

- Halothane.
- Suxamethonium.
- Methoxyflurane and enflurane.
- Cyclopropane.
- Phencyclidine.
- Ketamine.

Halothane and succinylcholine account for 80% of cases.

Box 9.33 Drugs considered safe in malignant hyperthermia

- Barbiturates.
- Nitrous oxide.
- Benzodiazepines.
- Opiates.
- Pancuronium.
- Antibiotics.
- Antihistamines.
- Local anaesthetic agents.

Diagnosis

- Malignant hyperthermia most commonly presents in patients in their early 20s. Early signs are muscular rigidity, sinus tachycardia and SVTs, ↑ carbon dioxide production with tachypnoea, and hypertension. Patients may sweat profusely and exhibit skin mottling.
- Hyperthermia occurs late and may be rapidly followed by hypotension, mixed respiratory and metabolic acidosis, and hyperkalaemia, which gives rise to VT and cardiac arrest.
- The condition almost always occurs perioperatively.
- The differential diagnosis includes phaeochromocytoma, thyrotoxic crisis, narcotic-induced hyperthermia in patients taking MAOIs, and drug-induced hyperthermia [caused by cocaine, phencyclidine, amphetamine,

lysergic acid diethylamide (LSD), tricyclics, and aspirin], and certain infections such as malaria.

- Plasma CPK is high, as is myoglobin. Urine may therefore appear dark.
- DIC is a further late manifestation.

Treatment

The aim of therapy is to decrease thermogenesis and promote heat loss.

- **Dantrolene:** 1–2mg/kg IV every 5–10min to a maximum dose of 10mg/kg. Infusions should be repeated until cardiovascular and respiratory symptoms stabilize.
- Stop any trigger/anaesthetic agent.
- External surface cooling is helpful. All administered fluids should be chilled. Can stop once achieve a temperature $<38.5^{\circ}\text{C}$.
- Hyperventilate the patient with 100% O_2 if under anaesthesia.
- Patients should be managed on ITU with central venous access, an arterial line, and a urinary catheter.
- Treat hyperkalaemia with insulin/glucose, calcium chloride, and dialysis, if necessary.
- Consider bicarbonate for acidosis, under expert guidance.
- Procainamide should be given to all patients to prevent ventricular dysrhythmias (increases uptake of Ca^{2+} and may reduce hyperthermia). Alternative treatment of arrhythmias includes amiodarone and β -blockers.
- Hypotension should be treated with saline or colloids with isoprenaline. Dopaminergic and α -adrenergic agonists reduce heat dissipation and should be avoided.
- Some authorities advocate prophylactic anticonvulsants, as seizures are common.

For management key points on malignant hyperthermia, see Box 9.34.

Box 9.34 Management key points: malignant hyperthermia

- Early recognition and institution of therapy are key.
- Stop the trigger.
- Cool the patient, and start dantrolene 1–2mg IV, followed by infusions as necessary.
- Supportive measures, including management of hyperkalaemia.
- Screening of family members is important in suspected malignant hyperthermia.

Further reading

Glahn KP, Ellis FR, Halsall PJ, et al. Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group. *Br J Anaesth* 2010;105:417–20.

Neuroleptic malignant syndrome

The neuroleptic malignant syndrome results from an imbalance of dopaminergic neurotransmitters following neuroleptic drug use (see Box 9.35). The incidence is 0.5% in patients taking neuroleptic drugs. This syndrome is clinically distinct from malignant hyperthermia (➡ Malignant hyperthermia, pp. 602–3); it is not an allergic reaction. The mean age of onset is 40 years. Mortality is 10–20%.

Clinical features

- Muscular rigidity, including dysphagia, dysarthria—early (96%).
- Extrapyramidal signs (pseudo-parkinsonism), tremor (90%).
- Oculogyric crisis.
- Catatonia: muteness (95%).
- Altered consciousness or coma.
- ↑ serum CPK/AST (97%).
- Pyrexia (rarely >40°C) follows onset of rigidity.
- Autonomic instability, including tachyarrhythmias, labile BP, sweating, and tachypnoea.

The syndrome can occur within hours of initiating drug therapy but typically takes ~1 week. It can also occur following a dosage increase of a well-established drug.

Complications

- Rhabdomyolysis (➡ Rhabdomyolysis, pp. 306–7), with raised CK.
- Electrolyte disturbance, including hypocalcaemia, hypomagnesaemia, and hyperkalaemia.
- Metabolic acidosis, often with raised lactate.
- Renal (15%) and hepatic failure.
- Fitting—rare.
- Cardiovascular collapse.
- DIC.
- Respiratory failure.

Differential diagnosis

- Malignant hyperthermia (➡ Malignant hyperthermia, pp. 602–3).
- Serotonin syndrome.
- Heat stroke.
- CNS infections or vasculitides.
- Other causes of catatonia.
- Thyrotoxic crisis (➡ Thyrotoxic crisis: assessment, p. 586).
- Pheochromocytoma (➡ Pheochromocytomas: assessment, pp. 596–7).
- Drug-induced hyperthermia (caused by cocaine, LSD, phencyclidine, amphetamine, tricyclics, and aspirin).

Management

(See Box 9.36.)

- Withdrawal of causative agent (unless the precipitant is withdrawal of the dopaminergic agent, in which case it should be reinstated).
- Admission to ITU.

- Dantrolene (1–2mg/kg every 6h, up to a maximum 300mg/day).
- Paralysis and ventilation (curare, pancuronium).
- Antiarrhythmics, as necessary.
- Fluid resuscitation for raised CK or rhabdomyolysis.
- Treat hyperthermia with cooling blankets. Consider paracetamol use.
- Thromboprophylaxis.
- Bromocriptine, amantadine, levodopa (increase dopaminergic tone and reduce rigidity, thermogenesis, and extrapyramidal symptoms). Most agents are used on the basis of experience or anecdotal evidence, with little supporting evidence. The condition carries high morbidity and mortality.

Box 9.35 Drugs associated with neuroleptic malignant syndrome

- Haloperidol.
- Phenothiazines.
- 'Atypical' antipsychotics (clozapine, olanzapine, risperidone) less commonly with these drugs, but still occasionally seen.
- Metoclopramide.
- Tetrabenazine.
- Thioxanthenes.
- Withdrawal of levodopa or amantadine.

Box 9.36 Management key points: neuroleptic malignant syndrome

- Consider the diagnosis if symptoms of rigidity, fever or dysautonomia occur in the setting of neuroleptic use.
- Exclude other important differential diagnoses including CNS infections and vasculitides.
- Withhold neuroleptic agents.
- Admit to ITU and institute supportive measures especially for dysautonomia. Be vigilant for complications.
- Consider use of dantrolene, bromocriptine or amantadine.

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Blood transfusion reactions

Assessment

See Table 10.1.

Table 10.1 Blood transfusion reactions: assessment

Presentation	Causes	Timing
<i>Shock (major haemolysis)</i>	Red cell antibodies	Immediate
Lumbar or loin pain, headache	ABO incompatibility	(min/h)
Chest pain, shortness of breath	Other antibodies	
Rigors, pyrexia		
Urticaria, flushing		
Hypotension		
Oliguria		
Haemoglobinuria		
Jaundice		
DIC		
<i>Shock (septic)</i>	Bacterial contamination	Immediate
Rigors, pyrexia		(min/h)
Hypotension		
Oliguria		
DIC		
<i>Fever</i>	White cell antibodies	Early
Isolated pyrexia	Recipient cytokines	(30–90 min)
Rigors		
<i>Allergic reactions</i>	Donor plasma proteins	Early
Urticaria	(more common with plasma or platelets)	(min/h)
Pyrexia		
Rigors		
Facial oedema		
Dyspnoea		
<i>Transfusion-associated circulatory overload (TACO)</i>	Rapid/over-transfusion in low-weight patient: aim for 4mL/kg	Early
Breathlessness		(h)
Cough		
Oedema		

Table 10.1 (Contd.)

Presentation	Causes	Timing
<i>Transfusion-related acute lung injury (TRALI)</i> Non-cardiogenic pulmonary oedema Pyrexia Cough Breathlessness CXR changes	Donor white cell antibodies (rare)	Early (min/h)
<i>Delayed haemolysis</i> Pyrexia Anaemia Jaundice	Minor red cell antibodies	Late (7–10 days)
<i>Delayed thrombocytopenia</i> Purpura Mucosal bleeding	Platelet antibody (commonly anti-PI ^{A1})	Late (2–10 days)
<i>Infection</i>	Hepatitis B/C, non-A/B/C, CMV, EBV, HIV, HTLV, toxoplasmosis, malaria, syphilis	Late (days/months)

Management

The main problem encountered in practice is differentiating a (common) rise in temperature during a blood transfusion from (the rare, but potentially lethal) major transfusion reactions. The common patterns of reactions are outlined in Table 10.1.

Pointers to a severe reaction include:

- Symptoms: does the patient feel unwell?
- Pattern of temperature: a *rapid* rise in temperature to $>38^{\circ}\text{C}$ is common in minor reactions.
- Hypotension or tachycardia.

(See Table 10.2 for the management of blood transfusion reactions.)

Table 10.2 Management of blood transfusion reactions

Reaction	Management
Isolated pyrexia	Slow transfusion Give paracetamol Finish transfusion if no progression of symptoms
Urticarial reaction	Slow transfusion Give chlorphenamine 10mg IV Complete transfusion if no progression of symptoms Sometimes patients need hydrocortisone 100mg IV
Shock Anaphylaxis ABO incompatibility Septic shock	Stop transfusion and give O ₂ Give adrenaline 0.5–1mg SC, and consider repeating every 10min until improvement. Contact duty anaesthetist and ITU for haemofiltration if AKI Give chlorphenamine 10mg IV (and crystalloid; consider inotropes) Monitor fluid balance. Take blood: FBC, U&Es; full coagulation screen (for DIC); repeat cross-match and direct antigen test (DAT); return donor blood Urine: bilirubin, free Hb
Circulatory overload (➡ Pulmonary oedema: assessment, pp. 92–3)	O ₂ , furosemide IV (40–120mg) Nitrate infusion (0–10mg/h)
TRALI	Life-threatening. Treat as ARDS (➡ Adult respiratory distress syndrome 1, p. 204)
Delayed haemolysis	Report to blood bank Repeat cross-match and DAT Transfuse with freshly cross-matched blood
Thrombocytopenia	Immune-mediated: treat with PI ^{HL} -negative transfusions, high-dose IV IgG, steroids, and plasmapheresis (dilutional ↓ platelets seen if >5U transfused)

Report any serious or haemolytic reaction to a haematologist.

Sickle-cell crisis: presentation

A small percentage of sufferers with sickle-cell disease have recurrent crises and repeated hospital admissions. There is an unwarranted tendency to attribute this to a low pain threshold or to 'dependence' on opiates, rather than to the severity of disease. Analgesia should never be denied to patients. This group of patients has the highest rate of serious complications and mortality as a result of their severe disease. Sudden death is still a major problem.

Painful (vaso-occlusive) crisis

- This is the most common presentation in adults and children.
- Severe/excruciating pain is felt at one or more sites, especially long bones (small bones in children), back, ribs, and sternum.
- There may be associated pyrexia (usually $<38.5^{\circ}\text{C}$), tenderness, local warmth, and swelling, or there may be no objective features.
- Haemolysis may be $\uparrow$ ($\uparrow$ bilirubin, $\uparrow$ LDH, fall in Hb) but is not a good correlate.
- *There are no reliable clinical markers for the severity of a crisis.*

Chest crisis

- The most common cause of mortality.
- Vaso-occlusion of the pulmonary microvasculature results in reduced perfusion and local infarction.
- May be heralded by rib/sternal pain and/or falling SpO_2 .
- May be precipitated by a chest infection, pregnancy, surgery, and in smokers.
- Prevented by: increasing HbF, with hydroxycarbamide, and incentive spirometry.
- Symptoms (which may be minor initially) include pleuritic chest pain and breathlessness.
- Signs are variable (often minimal) but can progress rapidly; usually reduced air entry at lung bases.
- CXR is variable: uni-/bilateral consolidation, usually basal; 'white-out'; minimal changes.
- PaO_2 is often markedly reduced. NB O_2 delivery is low, given anaemia.

Cerebral infarction

- Usually in children <5 years, rare in adults.
- Presents as acute stroke.
- High risk of recurrence.

Splenic/hepatic sequestration

- Usually in children <5 years.
- RBCs trapped in the spleen and/or liver, usually causing organomegaly.
- Causes severe anaemia; circulatory collapse.

Aplastic crisis

- Usually in children, young adults.
- Mainly caused by parvovirus infection, exacerbated by folate deficiency.
- Occasionally when hydroxycarbamide dose has $\uparrow$.
- Sudden fall in Hb, inappropriately reduced/normal reticulocyte count.

Haemolytic crisis

- Often accompanies painful crises.
- Exacerbated by medications, including in those with G6PD (even in ♀).
- Fall in Hb; ↑ reticulocyte count.

Cholecystitis/cholangitis/biliary colic

- Pigment stones common due to haemolytic anaemia and genetic predisposing polymorphism associated with Gilbert's syndrome.
- Can be misinterpreted as vaso-occlusive crisis.

Priapism

- Prolonged, painful erections due to local vaso-occlusion (1–24h long).
- Major crisis often preceded by 'stuttering' priapism episodes.
- May result in permanent impotence.
- This is a urological emergency. On-call urologists should be informed on the patient's arrival in casualty.

Infections/septic shock

- Any age group.
- Fever may not be prominent, and hypotension is a late sign in children.
- Osteomyelitis may not be apparent and may mimic veno-occlusive crises and complicate leg ulcers.
- Patients receiving iron chelation therapy are at risk of *Yersinia* spp.
- Patients with long-term venous access devices (e.g. Portacath) are at risk of Gram +ve infections.

Sickle-cell crisis: management

General measures

See NICE guidelines CG143¹.

See Box 10.1 for management key points in sickle-cell crises.

Control pain

- This should be individualized; seek expert haematology input.
- Assess pain objectively with a score to assess treatment response.
- Have a low threshold to investigate for causes of pain not attributable to veno-occlusive disease, especially if atypical for the patient.
- Usually parenteral opiates are necessary, often in high doses (depending on previous opiate exposure). Start low and review in 0.5h, titrating to response, e.g.
 - Morphine 5–40mg IM every 2h.
 - Diamorphine 5–25mg SC every 2h.
- Failure to control pain using these regimens usually indicates the need for a continuous opiate infusion or a patient-controlled analgesia (PCA) pump. Some patients prefer pethidine, but there is a risk of seizures as the drug metabolites accumulate.
- Oral analgesia (dihydrocodeine/NSAIDs) may be sufficient for minor crises, with regular paracetamol (IV preferred initially).
- Supplementary analgesics, such as diclofenac 50mg tds PO, may have a small additional benefit.

Ensure hydration

- IV crystalloids are preferred, but venous access may be a problem.
- Aim for an input of 3–4L/day, with close monitoring of balance.
- Fluids can be oral where venous access is problematic.

Give oxygen

- Not of proven benefit (except in chest crises), but often provides symptomatic relief.
- Incentive spirometry prevents chest crises.
- Monitor O₂ saturations on air and O₂; falling sats may be an early indication of a chest crisis.
- In a severe chest crisis, CPAP/full ventilation may become necessary. Transfer to ITU early.

Give folic acid

Give 5mg PO od (continue long term in all patients).

Review sources of sepsis

- Infections are frequent (at least partly due to hyposplenism).
- Penicillin prophylaxis and vaccination [pneumococcal, *Haemophilus influenzae* b (Hib), meningococcal, influenza] do reduce the incidence, but some penicillin-resistant organisms are emerging.
- If an infective precipitant, or component, of the crisis is suspected, start 'blind' antibiotics (e.g. cefuroxime 750mg IV tds) after an infection screen.
- Consider less common sources of sepsis (e.g. osteomyelitis, *Mycobacterium*, etc.).

Give thromboprophylaxis

LMWH prophylaxis should be used routinely.

Give other supportive therapy

Laxatives, antiemetics, and anti-pruritics with opiates.

Investigations

(See Table 10.3.)

Table 10.3 Investigations in sickle-cell crisis

Investigation	Comment
FBC	Hb (? fall from steady state), WCC (neutrophilia common)
Reticulocytes	Raised in haemolysis, reduced in aplastic crisis
HbS and HbF %	Can guide red cell exchange and hydroxycarbamide
Blood cultures	Even if not pyrexial, especially if hypoxic
Stool cultures	If diarrhoea (? <i>Salmonella</i> or <i>Yersinia</i> spp., osteomyelitis)
CXR	Regardless of symptoms
Pulse oximetry	All patients. ABG if hypoxic, otherwise venous blood gas
Bone X-ray	? osteomyelitis (persisting pain, pyrexia, or bacteraemia). ? avascular necrosis (chronic hip/shoulder pain). May need MRI if strong suspicion
Viral PCR	If aplastic crisis (? parvovirus)
Cross-match	If transfusion/exchange indicated (see ➡ Exchange transfusion, p. 615). Extended red cell phenotyped transfusion

Exchange transfusion

The exchange can be performed on a cell separator. Aim for Hb of between 70 and 90g/L (end haematocrit of 0.34) in either case; *a higher Hb can increase blood viscosity and precipitate further sickling*. In severe crises, red cell exchange should be repeated until the HbS % is <30%. If a larger exchange is not required or fluid balance is not precarious, manual venesection of 1–2U can be performed. Fluid replacement (normal saline 1L over 2–4h), followed by transfusion of extended phenotype cross-matched blood.

Indications for urgent exchange transfusion

- Chest crisis.
- Cerebral infarction.
- Severe, persisting painful crisis.
- Priapism.
- Organ failure.
- Refractory ulceration.
- Preoperative.

Box 10.1 Management key points: sickle-cell crisis

- **Analgesia:** parenteral morphine (10–40mg IM 2-hourly) or diamorphine (10–25mg SC 2-hourly). If these fail, use continuous opiate infusion or a PCA pump. Oral dihydrocodeine/NSAIDs for most cases.
- **IV fluids:** aim for an input of >3L of crystalloid/day, if not compromising oxygenation.
- **Oxygen:** for all patients. CPAP/ITU care in a severe chest crisis/invasive ventilation.
- **Folic acid:** 5mg PO od.
- **Antibiotics:** if an infective precipitant is suspected (start 'blind' antibiotics, e.g. co-amoxiclav or piperacillin with tazobactam IV with clarithromycin, after an infection screen).
- **Exchange transfusion** (see ➡ Exchange transfusion, p. 615).

References

1. National Institute for Health and Care Excellence (2012). *Sickle cell disease: managing acute painful episodes in hospital*. Clinical guideline [CG143]. <https://www.nice.org.uk/guidance/CG143>

Bleeding disorders: general approach

Presentation

- Normal haemostasis requires the interaction of platelets, fibrin from the clotting cascade, and the microvasculature. An abnormality of any of these components may present as easy bruising, purpura, or spontaneous or excessive bleeding.
- Muscle haematomas or haemarthroses suggest clotting factor deficiencies (e.g. haemophilia) whereas purpura, minor bruising, or epithelial bleeding suggest abnormalities of platelet function, collagen, or primary haemostasis.
- Mucosal haemorrhage (acute GI bleed) may occur without any haemostatic abnormalities, e.g. due to peptic ulcer disease.
- If a coagulation or platelet abnormality is uncovered on 'routine' testing, examine the patient for occult bleeding (e.g. iron-deficient anaemia, fundal haemorrhages).
- A personal or family history of excess bleeding may suggest a congenital haemostatic problem—expert haematology input is essential.

Causes

These can be divided into:

- Coagulation abnormalities.
- Platelet abnormalities (too few or dysfunctional).
- Microvascular/collagen abnormalities.

Investigations

All patients should have

- Coagulation screen [PT, APTT, thrombin time (TT), fibrinogen].
- von Willebrand factor (vWF) Ag, factor XIII, ristocetin cofactor (RiCof).
- FBC and film.
- U&Es.
- LFTs.
- Cross-match.

Where appropriate, consider

- Platelet function tests.
- 50:50 or 80:20 plasma mixing assays.
- Specific coagulation factor levels.
- Acquired factor inhibitors.
- vWF multimer gels.
- PFA-100.
- Thromboelastography (TEG®)/ROTEM®.
- Genetic tests/gene sequencing.
- Bone marrow aspirate and trephine.
- Bleeding time (only for collagen defects).

Management

General measures

- Avoid non-steroidal medications, especially aspirin.
- Do not give IM injections.
- Avoid arterial or lumbar punctures.
- Enlist expert help with invasive procedures. Use the internal jugular, rather than the subclavian, route for central line insertion with US.

- Examine the skin, oral mucosa, and fundi for evidence of fresh bleeding.
- Restore circulatory volume with IV crystalloid (colloids exacerbate bleeding) if there is haemodynamic compromise, and consider blood component transfusion.

Specific therapy

- Look for any local cause for the bleeding (e.g. oesophageal varices, vascular damage causing epistaxis, chest infection causing haemoptysis) that may be amenable to treatment.
- Stop any drug that may be exacerbating the bleeding (see Box 10.2).
- Correct coagulation abnormalities, if appropriate (➡ Abnormal coagulation 1, p. 620).
- Correct platelet abnormalities, if appropriate (➡ Abnormal platelets, pp. 622–3).

Box 10.2 Drugs that may cause bleeding disorders

Coagulation abnormalities

- Heparin.
- Coumarins (e.g. warfarin).
- Thrombin inhibitors (dabigatran, hirudin).
- Factor Xa inhibitors (rivaroxaban, apixaban).

Thrombocytopenia

Immune

- Heparin.
- Quinine.
- Penicillin.
- H₂-receptor antagonists.
- Thiazide diuretics.

Non-immune

- Cytotoxic chemotherapy.
- Chloramphenicol.
- Primaquine.
- Alcohol.

Abnormal platelet function

- Aspirin, NSAIDs.
- Clopidogrel.
- Antibiotics (e.g. piperacillin, cefotaxime).
- Colloids/dextrans.
- SSRIs.
- Alcohol.

Abnormal microvasculature

- Corticosteroids.

Abnormal coagulation 1

Common causes

- Anticoagulants.
- Liver disease.
- DIC.
- Massive transfusion.

Rarer causes

- Haemophilia A (acquired or congenital) and B.
- von Willebrand’s disease (vWD) (acquired or congenital).
- Amyloid (acquired factor X or IX deficiency with vasculopathy).
- α_2 -antiplasmin deficiency.
- Vitamin K deficiency:
 - Obstructive jaundice.
 - Small bowel disease.

Diagnosis

(See Table 10.4.)

Table 10.4 Diagnosis of abnormal coagulation*

Defect	Interpretation	Consider
↑ PT	Extrinsic pathway defect	Warfarin, liver disease, vitamin K deficiency, factor VII deficiency
↑ APTT	Intrinsic pathway defect	Heparin, haemophilia A or B, vWD, lupus anticoagulant (antiphospholipid syndrome)
↑ PT and APTT	Multiple defects (usually acquired)	Liver disease, DIC, warfarin, factor V and/or X deficiencies, factor Xa inhibitor anticoagulation
↑ TT	Abnormal fibrin production	Heparin effect, fibrinogen defect, excess fibrin degradation products (FDPs) (which interfere with reaction). Reptilase time* will be normal if due to heparin
↑ PT, APTT, TT	Multiple (acquired) defects	Deficient or abnormal fibrinogen or heparin. Factor IIa inhibitor anticoagulation
↓ fibrinogen	Excess consumption of clotting factors and fibrinogen	Consumptive coagulopathy (but not necessarily full DIC), hyperfibrinolysis, severe liver disease
↑ FDPs	↑ fibrin(ogen) degradation	The exact interpretation depends on the lab test used. Some do not distinguish between fibrin and FDPs. Some are more specific to fibrin degradation (e.g. D-dimers) and are therefore suggestive of widespread clot formation and breakdown (i.e. DIC)
PFA-100	Abnormal platelet function	Congenital or acquired platelet dysfunction. Consider further platelet function studies (aggregation; electron microscopy), vWD (↑ APTT)

The lupus anticoagulant usually confers a prothrombotic, rather than a bleeding, tendency.

* Reptilase is a snake venom not inhibited by heparin. It converts fibrinogen to fibrin.

Abnormal coagulation 2

Management

Options are:

- **FFP:** indicated for treatment of acute DIC with bleeding, improving haemostasis in decompensated liver failure if bleeding or prior to a procedure, and emergency reversal of warfarin therapy if no PCC available. Give 15mL/kg, i.e. 4–5U (~200mL/U). Watch for signs of fluid overload, and give IV furosemide, if necessary.
- **Vitamin K:** phytonadione 5–10mg IV slowly (daily for 3 days) if deficiency is suspected; 2–5mg IV/PO will improve over-warfarinization in 6–12h if no bleeding with low INR; 0.5–1mg for minor adjustment.
- **Protamine sulfate** (1mg IV neutralizes 100IU of heparin): is rarely used in practice. Stopping a heparin infusion will normalize the APTT in 2–4h.
- **Cryoprecipitate or fibrinogen concentrate:** should be considered if fibrinogen level is below 1–1.2g/L.
- **Factor concentrates:** can be used in the treatment of isolated factor deficiencies, e.g. haemophilia A. Concentrates of factors II, VII, IX, and X are also available in some centres for specific reversal of warfarin effects (PCC).
- **Antifibrinolytics:** are used for the treatment of life-threatening bleeds following thrombolytic therapy or major surgery (e.g. cardiac surgery or prostatectomy), and in certain conditions associated with hyperplasmaemia (e.g. acute promyelocytic leukaemia, certain malignancies). Give tranexamic acid 0.5–1g slow IV injection tds.
- **Miscellaneous:** desmopressin and oestrogens are occasionally used for haemophilia and renal failure.

Circulating inhibitors of coagulation

Lupus anticoagulant

- Causes prolonged APTT but predisposes to thrombosis, not bleeding (antiphospholipid syndrome); 50:50 mixing studies do not correct the prolonged APTT.

Acquired haemophilia A/vWF

- Elderly patients presenting with severe bruising and prolonged APTT.
- Pregnancy.
- Patients with aortic stenosis.
- Discuss with haematologists.
- 50:50 or 80:20 mixing studies do not fully correct the prolonged APTT.

Abnormal platelets

Causes

Thrombocytopenia
(See Table 10.5.)

Table 10.5 Thrombocytopenia

Increased platelet consumption	Reduced platelet production
● Immune: • Idiopathic (ITP) • Drug-induced • SLE • HIV-related ● Non-immune: • Massive transfusion • Hypersplenism • DIC, TTP	● Myelosuppressant: • Drugs, alcohol • Viral infections ● Marrow infiltration/failure ● B₁₂ or folate deficiency ● ITP (one-third of cases) ● Inherited disorders (rare)

Abnormal platelet function

- Drugs (e.g. aspirin, clopidogrel).
- Uraemia.
- Liver disease.
- Myeloproliferative disorders.
- Myelodysplasia.
- Dysproteinaemia (e.g. myeloma).
- Inherited disorders (rare):
 - Glanzman’s disease (GP IIb/IIIa deficiency).
 - Bernard–Soulier (GP deficiency).
 - Chediak–Higashi syndrome (abnormal platelet granules).
 - Grey platelet syndrome (α granule deficiency).
 - Storage pool disease.
 - Secretion defect.

Investigations

- *Peripheral blood film*: evidence of haemolysis (? DIC, ? TTP) or marrow infiltration. Abnormal platelet size. Grey platelets.
- *Coagulation screen*: ? DIC.
- *Autoantibody screen*: associated autoimmune diseases.
- *Bone marrow aspirate*: ↑ megakaryocytes generally indicate peripheral consumption; ↓ or abnormal megakaryocytes suggest a marrow problem. Dysplasia. Micromegakaryocytes.
- *Antiplatelet antibodies*: rarely indicated or useful.
- *Platelet function tests*: for bleeding in the presence of adequate platelet numbers on the blood film.

- *Low platelets* ($<10 \times 10^9/\text{L}$) may cause spontaneous bleeding and require platelet transfusion $\pm$ treatment for the underlying cause; <20 if sepsis present.
- *Moderately low counts* ($20\text{--}140 \times 10^9/\text{L}$) will rarely cause spontaneous bleeding, unless there is an associated clotting abnormality (e.g. DIC) or a primary marrow defect, with production of defective platelets (e.g. myelodysplasia). Transfuse only if there is continued bleeding or in preparation for major surgery.
- *High counts* ($500\text{--}1000 \times 10^9/\text{L}$) may also indicate a primary production problem, with abnormal platelets (e.g. myeloproliferative disorders). (NB A moderately raised platelet count is a normal response to bleeding and iron deficiency, and is also seen in chronic inflammation.)

Management

This depends on the platelet count and severity of bleeding.

Immune-mediated thrombocytopenia

- Platelet transfusions are usually ineffective as sole therapy and rarely indicated, unless severe bleeding or urgent surgery required.
- Ig 0.4g/kg/day IVI for 5 days (or 2g/kg/day for 1–2 days): this usually works quicker than steroids, but the effect only lasts 2–4 weeks. Start the infusion very slowly, as anaphylactic reactions (fever, urticaria, bronchospasm, and hypotension) are not uncommon.
- Prednisolone (1mg/kg od) is the standard first-line treatment for adult ITP.
- Dexamethasone.

Acute DIC/massive transfusion

- Give platelet transfusions to maintain platelet count $>30\text{--}50 \times 10^9/\text{L}$ (for chronic DIC, transfuse only for active bleeding).

Surgery

- Depends on the surgery, but generally aim for platelet count $>50 \times 10^9/\text{L}$.
- For CNS surgery or multiple trauma, aim for count $>100 \times 10^9/\text{L}$.

Reduced platelet production (chronic, stable)

- If no bleeding, transfuse if count $<10 \times 10^9/\text{L}$.

TTP/heparin-induced thrombocytopenia

- Platelet transfusions are contraindicated. Discuss all cases with the haematologists.

Platelet transfusion

- A single unit is either a pool of four buffy coats or platelets from a single ♂ donor from apheresis.
- The number of platelets in a unit is $<240 \times 10^9$ which is sufficient for most indications, unless there is ongoing consumption (e.g. severe DIC).
- If no consumption, platelets survive 2–5 days in circulation.

Anticoagulant therapy

(See Table 10.6.)

Table 10.6 Anticoagulant therapy, targets, and monitoring

Routes	Anticoagulant drug	Inhibitory targets	Potential assays
PO	Warfarin	Factor II, factor VII, factor IX, factor X, protein S, protein C	INR, PT
PO	Dabigatran	Factor IIa	Anti-IIa, TT, ecarin clotting time (ECT)
PO	Rivaroxaban	Factor Xa	Anti-Xa
PO	Apixaban	Factor Xa	Anti-Xa
IV or SC	Heparin (UF)	Factor IIa and Xa	APTT, anti-Xa, anti-IIa
IV or SC	Enoxaparin (LMWH)	Factor Xa > factor IIa	Anti-Xa
IV or SC	Danaparoid	Factor Xa	Anti-Xa
IV	Argatroban	Factor IIa	APTT, activated clotting time (ACT), ECT, anti-IIa
IV	Bivalirudin	Factor IIa	APTT, ACT, ECT, anti-IIa
SC	Other heparins (LMWH)	Factor Xa > factor IIa	Anti-Xa
SC	Fondaparinux	Factor Xa	Anti-Xa

Vitamin K antagonist oral anticoagulants: warfarin

- Warfarin overdose (accidental or deliberate self-harm) results in a prolonged PT (and thus INR), and sometimes lesser prolongation of APTT.
- Risk factors for significant bleeding include poor control, local lesion (e.g. peptic ulcer, angiodysplasia of the colon), high INR, coexisting haematological abnormality (e.g. thrombocytopenia, myelodysplasia, etc.).

Management

(Adapted from British Society for Haematology guidelines.)

- Major bleeding requires urgent correction of coagulation and drug cessation, regardless of the vitamin K antagonist: warfarin, phenprocoumon, acenocoumarol, phenindione. Discuss with a haematologist. PCC (purified factors II, VII, IX, and X) 25–50U/kg IV with 5mg of vitamin K IV. FFP 15mL/kg should only be used if prothrombin complex not available.
- Non-major bleeding requires 1–3mg of vitamin K IV.
- Moderate warfarin overdose (INR 5–8) without overt bleeding does not usually require specific treatment, and the patient may be managed as an outpatient. Withhold warfarin until the INR falls to the therapeutic range. Try to identify the cause (incorrect tablets, alcohol binge, etc.).
- Asymptomatic patients with INR >8 are given vitamin K 1–5mg PO (phytomenadione), with a repeat INR check the next day in case further vitamin K is needed. Reintroduce warfarin when INR <5.

- Asymptomatic patients with INR >5 should have warfarin withheld for 1–2 doses, and the maintenance dose should be reduced. The cause for the elevated INR should be addressed.

Non-vitamin K antagonist oral anticoagulants

Renal impairment and drug interaction may exacerbate bleeding. Actively look for occult GI bleeding in the presence of bleeding elsewhere due to a NOAC. See Table 10.7 for possible coagulation screen results with NOACs.

- Stop the NOAC; activated charcoal can be used if ingested within 1–2h.
- PCC 50U/kg can be used, with variable success, with other haemostatic measures and agents for major bleeding.
- In addition, dialysis and/or idarucizumab can be used for the direct thrombin inhibitor dabigatran reversal, and andexanet for factor Xa inhibitor reversal.
- A normal PT for factor Xa inhibitors (rivaroxaban or apixaban) or a normal TT (or APTT) for the direct thrombin inhibitor dabigatran usually indicates a low drug activity level with most reagents.
- A normal dilute TT (or ECT) in the presence of a direct thrombin inhibitor (dabigatran), or a normal anti-Xa activity in the presence of a factor Xa inhibitor (rivaroxaban or apixaban), usually indicates subclinical levels that do not require specific reversal therapy.
- Half-lives in descending order from up to 17h to 9h: dabigatran, rivaroxaban, apixaban.
- NOACs are contraindicated when the creatinine clearance is <15mL/min (or <30mL/min for dabigatran), for metal cardiac valves, and during pregnancy and lactation.

Table 10.7 Possible coagulation screen results with NOACs

Assay	Dabigatran	Rivaroxaban or apixaban
PT	↑/↔	↑/↔
APTT	↑	↑/↔
TT	↑	↔
Anti-Xa	–	↑
ECT	↑	–

Heparin

Risk factors for bleeding include age, recent surgery or trauma, renal or liver failure, malignancy, APTT ratio >3, and a coexisting haematological abnormality.

Management

- *Stop heparin*: the APTT usually normalizes in 2–4h.
- *Protamine sulfate* (1mg IV neutralizes 100U of heparin): may be used; halve the dose if heparin has been turned off 1h previously.
- *LMWHs*: are thought to have fewer bleeding complications. However, their plasma half-life is longer and they are less effectively reversed with protamine. Treatment of OD is as described earlier, but note that the APTT is usually normal on LMWH.
- Heparin-associated thrombocytopenia (⊖ Abnormal platelets, pp. 622–3).

Bleeding with fibrinolytic therapy

Risk factors for bleeding with fibrinolytic therapy are given under ➡ STEMI: thrombolysis 2, pp. 24–5. Severe haemorrhage should be managed with:

- *Supportive measures* (blood transfusion).
- Cryoprecipitate or fibrinogen concentrate transfusion as a source of fibrinogen.
- *Tranexamic acid* (0.5–1g slow IV injection, tds) should also be given.

Bleeding in liver disease

The liver is involved in the synthesis of factors II, VII, IX, and X (the vitamin K-dependent factors) and the non-vitamin K-dependent factors (e.g. factor V), as well as in the clearance of 'activated' coagulation factors, fibrin molecules, and tissue plasminogen activator (tPA). The abnormalities most commonly found are:

- *Obstructive jaundice*: prolonged PT (vitamin K deficiency).
- *Acute liver failure*: prolonged PT and later prolonged APTT and TT (DIC).
- *Cirrhosis*: prolonged PT, APTT, and TT; low fibrinogen and/or dysfibrinogenaemia; raised FDPs, ↓ clearance of tPA; low platelets (hypersplenism, DIC, and marrow dysfunction).

Management

Treatment is required for active GI bleeding or as prophylaxis for surgery or liver biopsy.

- Give *vitamin K* 10mg IV slowly.
- *FFP transfusion* is more effective, but short-lived.
- Consider PCC (purified factors II, VII, IX, and X) for life-threatening bleeding, if fluid-overloaded. Liaise with haematology.

Bleeding in severe uraemia

Uraemia (usually $>35\text{--}50\text{mmol/L}$) results in both platelet dysfunction (impaired aggregation, adhesion, and activation) and endothelial dysfunction (exacerbated in the presence of amyloidosis).

Management

- The treatment of choice is haemodialysis.
- Other measures that have been shown to be effective include:
 - Cryoprecipitate infusion.
 - Desmopressin (➡ Haemophilia and related disorders 1, pp. 628–9).
 - Conjugated oestrogens.
 - Blood transfusion or erythropoietin to raise the haematocrit to >0.25 .

Massive transfusion/cardiopulmonary bypass

- Dilutional thrombocytopenia and coagulopathy usually occur once red cell concentrates equivalent to ~ 2 blood volumes have been transfused. With cardiopulmonary bypass, the extracorporeal circuit further damages the native platelets and depletes coagulation factors. Furthermore, cold temperature also inactivates platelets.
- Abnormalities include $\uparrow$ PT, $\uparrow$ APTT, $\uparrow$ FDPs, and $\downarrow$ fibrinogen.
- Post-transfusion thrombocytopenia is a distinct disorder seen 8–10 days following a transfusion and is due to a platelet-specific antibody (➡ Blood transfusion reactions, pp. 608–9).

Management

Treatment should be discussed with the haematology team and involves platelet transfusion to keep the platelet count $>50\text{--}75 \times 10^9/\text{L}$ (or $>100 \times 10^9/\text{L}$ for CNS lesions/multiple trauma), FFP (4–5U) if PT or APTT $>1.5 \times$ control, and cryoprecipitate (10–15U) if fibrinogen $<500\text{g/L}$.

Haemophilia and related disorders 1

Haemophilia A X-linked recessive (or acquired) deficiency of factor VIII (↑ APTT; ↓ factor VIII activity).

Haemophilia B X-linked recessive (or acquired) deficiency of factor IX (↑ APTT; ↓ factor IX activity).

Clinical presentation depends upon the degree of factor deficiency and whether inherited or acquired. If inherited:

- Patients with <1% activity (= severe disease) have a serious bleeding diathesis. Most are on home therapy.
- Patients with 1–5% activity are moderately affected; spontaneous bleeding is rare but should be treated as severe haemophiliacs when they do.
- Patients with 5–40% factor activity rarely bleed, unless there is trauma or surgery; mild disease.

Acute presentations

- *Acute haemarthroses*: often occur at sites of previous bleeding, particularly if this has led to degenerative joint disease. Ankles, knees, hips, and elbows are the most common sites. Symptoms include local tenderness, warmth, and swelling, and may take days or weeks to resolve.
- *Intramuscular bleeds*: can cause a compartment-type syndrome, leading to ischaemic necrosis and contracture. Iliopsoas bleed causes entrapment of the femoral nerve and produces the triad of groin pain, hip flexion, and sensory loss over the femoral nerve distribution. The pain may radiate to the abdomen and mimic appendicitis.
- *Intracranial bleeding*: is infrequent but is still a common cause of mortality. It often follows a minor head injury. Prognosis of intracerebral haemorrhage is generally poor. Extradural and subdural haemorrhage have a better prognosis.
- *Bleeding post-trauma*: classically, there may be an initial period of haemostasis; bleeding then becomes persistent or intermittent over days/weeks.
- *Haematuria/ureteric clot colic*: is rare in haemophilia. Usually there is no detectable underlying abnormality of the renal tracts.
- *Problems relating to coexisting HIV or hepatitis B/C infection*: are now the most common cause of mortality, due to infected factor VIII administered during the 1980s.

Investigations

Generally, acute investigations are not necessary for simple joint and muscle bleeds in a known haemophiliac. Consider:

- *USS*: for muscle haematomas (e.g. iliopsoas bleed).
- *CT scan*: history of head trauma, headache, abnormal neurology.
- *Factor VIII levels*: if bleed is severe and treatment is necessary.
- *Factor VIII inhibitor titre*: if refractory bleeds/history of inhibitor development.

von Willebrand's disease

- Autosomal dominant type 1 (quantitatively low levels), with varying expression, and type 2 (qualitatively low levels), or recessive (type 3).
- Reduced levels or abnormal function of vWF, which normally promotes platelet adhesion and protects factor VIII from destruction (hence ↓ factor VIII activity in severe disease).
- Less severe than the haemophilias, with haemarthroses and muscle bleeds being rare. Mucocutaneous bleeding (e.g. epistaxis, prolonged bleeding from cuts, heavy menstrual bleeding) and post-traumatic bleeding are the main problems.

Haemophilia and related disorders 2

Most patients contact their haematologist directly, unless they bleed when away from home. Be guided by your local haematologist.

General measures

- *Rest*: of the affected part and ice packs may be of benefit.
- *Analgesia*: avoid IM injections. Oral analgesia (e.g. dihydrocodeine) for minor bleeds; IV injections or infusions of high-dose opiates may be necessary. Use of NSAIDs is controversial.

Moderate or severe haemophilia

- Treat with IV factor VIII concentrate.

Mild haemophilia

- Factor VIII deficiency only: mild or moderate bleeds should be treated with desmopressin. Severe bleeds or those not responding to desmopressin: treat with IV factor VIII concentrate.
- Factor IX deficiency only: treat with factor IX.

von Willebrand's disease

- *Mild and moderate bleeds*: type 1—treat with desmopressin (except type 1C) + tranexamic acid. Type 2—usually requires vWF concentrate (typically an intermediate-purity factor VIII preparation).
- *Severe bleeds*: treat with vWF concentrate, and for type 3 vWD, consider platelet transfusions.

NB All CNS and perispinal bleeds are regarded as severe.

Factor VIII replacement

(See Table 10.8.)

- Minor bleeds may respond to a single slow IV bolus of factor VIII.
- Major bleeds: 12-hourly treatments (8-hourly in severe bleeding), with frequent monitoring of factor VIII levels, pre- and post-treatment.
- Patients with *factor VIII inhibitors* present a particular problem. This can sometimes be circumvented by the use of other products [e.g. factor VIII inhibitor bypassing activity (FEIBA) or recombinant activated factor VIIa].

Factor IX replacement

(See Table 10.8.)

- Plasma half-life is longer than factor VIII, and once-daily administration is sufficient (twice daily in severe bleeds).
- Avoid overdosage of factor IX, as it is highly thrombogenic.

Desmopressin

- **Indications:** mild to moderate haemophilia A, especially in children, vWD type 1 and some type 2. Most have previously responded to a challenge test dose.
- **Dosage:** 0.3 micrograms/kg in 100mL of normal saline IV over 30min; may be repeated 8–12h later. Alternatively, can be given SC at the same dose or intranasally (300 micrograms for an adult). Peak haemostatic effect in 60–90min.
- Monitor pulse and BP closely. Side effects include flushing, hypotension, tachycardia, headache, and nausea; rare reports of MI (caution in patients >60 years or with cardiac history). Temporary fluid restriction may be necessary (especially in children) due to ADH effects and risk of hyponatraemia.

Tranexamic acid

- Give with desmopressin in vWD or mild haemophilia A. Most useful in mucosal bleeds. Avoid in renal tract bleeding (may cause clots).
- **Dosage:** 1g PO qds (adults). Mouthwash 4.8% q10min for oral bleeding.

Cryoprecipitate

- Give for severe bleeding in vWD if vWF concentrate is not available and bleeding not responding to desmopressin and tranexamic acid.
- **Dosage:** 10–20U (bags) for 70kg adult.

Table 10.8 A rough guide for factor VIII and IX replacement

Condition	Desired factor level (IU/dL)	Dose of factor VIII (IU/kg)	Dose of factor IX (IU/kg)
Mild/moderate bleeds	50	25	65 = BeneFix® 40 = Replenine®
Major/life-threatening bleeds	100	50	130 = BeneFix® 80 = Replenine®

For example, a 70kg man with a minor bleed who is known to have haemophilia B and usually receives BeneFix® should receive $65 \times 70 = 4550\text{U}$ (round to the nearest vial = 4500U).

Combined thrombotic and haemorrhagic disorders

A group of disorders in which the pathways of haemostasis become deregulated, leading to microthrombus formation, platelet consumption, and, to a variable extent, clotting factor consumption. The exact pathogenesis varies, but in each case microthrombi cause organ damage, and thrombocytopenia and depleted clotting factors result in bleeding. This coexistence of thrombosis and bleeding makes management very difficult.

Disseminated intravascular coagulation

An inappropriate activation of coagulation, leading to:

- Depletion of clotting factors, causing *prolongation of PT and APTT*.
- Widespread thrombin activation, causing $\uparrow$ *TT* and $\downarrow$ *fibrinogen*.
- Formation of microthrombi, leading to *end-organ damage*.
- Destruction of RBCs in fibrin mesh, causing *microangiopathic haemolysis*.
- Consumption of platelets: *thrombocytopenia* increasing the bleeding tendency.
- Activation of thrombolysis (*raised FDPs*) and further bleeding.

The 'full house' of abnormalities does not need to be present initially, as the process is a progressive one. For causes, see Box 10.3.

Management

- *Treat the underlying cause* (60% have underlying sepsis).
- Supportive measures, such as correction of shock, acidosis, and hypoxia, may lead to an improvement in coagulopathy.
- Transfuse blood to correct anaemia. Massive transfusion may exacerbate coagulopathy by dilution of coagulation factors and platelets.

Product replacement

In acute DIC with bleeding, consider:

- FFP (15mL/kg, i.e. 4–5U) if PT or APTT $>1.5 \times$ control.
- 1U of platelets if platelet count $<50 \times 10^9/L$ or $<100 \times 10^9/L$ and rapidly falling.
- Cryoprecipitate (10–15U) or fibrinogen concentrate if fibrinogen $<500g/L$.
- Occasionally, IV heparin can stabilize severe DIC.
- Plasma exchange may rarely be considered.

Prognosis

In severe acute DIC, overall mortality is high. Obstetric complications have the best prognosis, if managed expediently. There is little evidence that measures to prevent thrombosis (heparin, antithrombin) or to prevent thrombolysis improve the general prognosis.

Box 10.3 Causes of DIC

Common

- Gram –ve septicaemia.
- *Staphylococcus aureus* sepsis.
- Meningococcal septicaemia.
- Malaria (especially *falciparum*).
- Disseminated malignancy:
 - Mucinous adenocarcinomas.
 - Prostatic carcinoma.
- Liver failure.

Rarer

- Incompatible blood transfusion.
- Severe trauma/burns.
- Acute promyelocytic leukaemia:
 - Obstetric emergencies.
 - Abruptio placentae.
 - Amniotic fluid embolism.
 - Retained dead fetus.
 - Severe pre-eclampsia.
- Anaphylaxis (e.g. snake bites).
- Hypoxia.
- Haemangioma.

Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome

Patients with classic TTP have been found to have an antibody against a metalloproteinase (ADAMTS-13) which cleaves very large multimers of vWF. These then accumulate and cause microthrombi and thrombocytopenia. The clinical picture tends to vary with age, with renal abnormalities being more common in children and neurological problems in adults, but with considerable overlap. In other similar thrombotic microangiopathies and HUS, the primary event appears to be endothelial damage causing microthrombus formation and end-organ damage. For causes, see Box 10.4.

Presentation

- TTP commonly occurs suddenly in a young or middle-aged woman, or following a viral infection.
- Fever.
- Anaemia (microangiopathic picture: associated with jaundice and haemoglobinuria).
- Thrombocytopenia with purpura; significant bleeding is rare.
- CNS (confusion, headache, meningitic symptoms, aphasia, visual disturbance, fits, coma, paralysis, psychoses—often fluctuating).
- Renal involvement (oliguria, anuria, haematuria), often mild initially.
- HUS is often preceded by gastroenteritis or URTI.
- Normal coagulation screen initially.

Investigations

(See Table 10.9 and Box 10.4.)

Table 10.9 Investigations in TTP and HUS

Investigation	Further comments
FBC	Anaemia with thrombocytopenia. Moderate leucocytosis with left shift
Blood film	Fragmented RBCs, polychromasia, thrombocytopenia
Clotting	Usually normal
U&Es	In adults, creatinine slow to rise over a few days; rapid deterioration more common in children
LFTs	↑ bilirubin (unconjugated). ↑ LDH (from haemolysis)
Haptoglobins	↓
Urinalysis	Proteinuria frequent; haematuria, haemoglobinuria
Stool	Culture, especially for <i>Escherichia coli</i> strains
ADAMTS-13 activity assay	Low activity

Box 10.4 Associations of TTP and HUS*Recognized*

- HIV infection.
- SLE.
- Normal pregnancy.
- Drugs (OCP, ciclosporin, quinine).
- Gastroenteritis (especially with *E. coli*, type 0157:H7 in children).

Controversial

- Coxsackie B infection.
- *Mycoplasma*.
- Malignancies.
- Bee stings.
- Radiotherapy.

Microangiopathic haemolytic anaemia

Management of HUS and TTP

- Refer to a specialist unit (haematology and/or renal).
- Plasma infusion with FFP while transferring to a centre for urgent plasma exchange.
- Urgent plasma exchange: solvent detergent-treated pooled plasma is currently recommended for TTP in the UK.
- Plasma exchange: aggressive regimen (40mL/kg/day) with FFP results in improvement of TTP in many patients (except post-BMT). Tail only after remission obtained. Start HAART if HIV-positive.
- Given 3 days of IV methylprednisolone.
- Most centres also give rituximab to reduce later recurrence.
- Dialysis (haemodialysis) is used for AKI (usually children).
- Broad-spectrum antibiotics: unproven benefit but seem sensible, given an infectious aetiology in some patients.
- Blood transfusion to correct anaemia.
- Platelet transfusion *contraindicated*; exacerbates thrombosis and may worsen the situation.
- Aspirin may be used once platelet count is $>50 \times 10^9/L$.
- Prophylactic LMWH is recommended when platelet count $>50 \times 10^9/L$ and solvent detergent-treated pooled plasma product is being used.
- Refractory TTP may respond to high-dose steroids, vincristine, or ciclosporin. Rituximab is increasingly being used.

Prognosis

- Children/predominant HUS picture: 5–30% mortality. Renal impairment and hypertension are common in survivors. Most adults require long-term haemodialysis.
- Adults/predominant TTP picture: 90% mortality if untreated; most die in first few days. With aggressive and early plasma exchange, mortality is now $<15\%$, but relapses are frequent and reduced with rituximab.

Heparin-induced thrombocytopenia and thrombosis (HITT)

- An idiosyncratic reaction seen in 1–5%. Much less common with LMWHs (<1%).
- Type I: mild and transient seen in the first week, often resolving spontaneously with continued therapy.
- Type II: late-onset thrombocytopenia seen 5 days to 2 weeks after starting therapy and is caused by an IgG autoantibody that results in platelet activation, and thromboembolic events in 40% if untreated.
- Bleeding is rare at presentation but will be ↑ because of the need for alternative anticoagulant therapy.
- Consider the diagnosis if the problem demanding heparinization does not resolve or worsens while the patient is on heparin (e.g. propagation of DVT) or a new thrombotic event takes place in a heparinized patient, in association with a >50% fall in platelet count.
- Diagnosis is based on the 4T scoring system (see Table 10.10).

The 4T score is the sum of the values for each of the four categories. Scores of 0–3, 4–5, and 6–8 are considered to correspond to a low, intermediate, and high probability of HIT, respectively.

Management

- HIT can be excluded by a low pretest probability score, without the need for laboratory investigation.
- If the pretest probability of HIT is not low, heparin should be stopped and an alternative anticoagulant started in full dosage, while laboratory tests are performed. Do not wait to see what happens to the platelet count.
- An alternative anticoagulant [e.g. danaparoid, argatroban, fondaparinux (pregnancy), bivalirudin (urgent PCI or surgery)] is usually indicated for 3 months in the presence of thrombosis and 1 month without thrombosis.
- LMWHs can have a crossover effect and perpetuate the problem.
- Do not start a coumarin (e.g. warfarin) until an alternative anticoagulant has been instated and the platelet count has normalized.
- Do not give platelets to treat thrombocytopenia, as this can lead to further platelet activation and thrombosis.
- Heparin re-exposure can occur after >3 months if the patient is IgG antibody-negative.

Table 10.10 The 4T scoring system*

4T category	2 points	1 point	0 points
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥ 20	Platelet count 30–50% or platelet nadir 10–19	Platelet count fall <30% or platelet nadir <10
Timing of platelet count fall	Clear onset days 5–10 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5–10 fall, but not clear (e.g. missing platelet counts); onset after day 10; or fall ≤ 1 day (prior heparin exposure 30–100 days ago)	Platelet count ≤ 4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction post-IV UFH bolus	Progressive or recurrent thrombosis; non-necrotizing (erythematous) skin lesions; suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

* Reproduced from Lo GK, et al. 'Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings'. *Journal of Thrombosis and Haemostasis*, 2006; 4: 759–65, with permission from John Wiley and Sons.

Acute leukaemias: presentation

Types of acute leukaemia

Acute leukaemia

- Acute leukaemia is defined using the World Health Organization (WHO) classification, which includes cytogenetic data and provides useful clinical and prognostic information.
- Acute myeloid leukaemia (AML).
- Traditional French-American-British (FAB) classification (M0–M7).
- Acute promyelocytic leukaemia (APL; M3) is often associated with DIC and a relatively low WCC.
- Monocytic differentiation often manifests with organ infiltration.
- WHO classification includes AML with characteristic genetic abnormalities, AML with multilineage dysplasia, and AML with myelodysplastic syndrome (MDS), therapy-related.
- Mainly adults, including the elderly.
- Acute leukaemias may occur *de novo* or may transform from chronic myeloid leukaemia [to 70% AML, 30% acute lymphoblastic leukaemia (ALL)]. MDS can also evolve into AML.
- ALL, usually precursor B-cell, and occasionally precursor T-cell, in origin (FAB L1-2). Burkitt's lymphoma (L3) is now separately classified.
- Acute biphenotypic leukaemia.

Poor prognostic factors

- Increasing age.
- High WCC at presentation.
- Prior MDS.
- Philadelphia chromosome-positive acute leukaemia (20% in adult ALL, 5% in children).
- Depends upon subclassification of leukaemia on the basis of morphology, chromosomal abnormalities, and cell surface markers.

Presentation

Red cell problems

- *Anaemia*: caused by replacement of normal erythropoiesis by leukaemia cells; also by bleeding due to low platelets or deranged clotting (APL). The MCV is usually normal or high (MDS), unless blood loss is predominant.

White cell problems

- *High blast count*: may cause 'leucostasis' (crudely, sludging of white cells in small vessels), causing respiratory impairment, myocardial ischaemia/MI, renal impairment, acute confusion, stroke, fits, and migraine.
- *Leukaemia-related phenomena*: pyrexia, malaise, muscle and joint pains.
- *Neutropenia*: secondary to marrow infiltration by leukaemic cells.

Platelet problems

- *Thrombocytopenia* due to myelosuppression by leukaemic infiltrate.
- Existing platelets may have sub-normal function. Risk of bleeding increases if platelets are $<10 \times 10^9/\text{L}$ or $<20 \times 10^9/\text{L}$ if there is concomitant sepsis or coagulation abnormality.

Coagulation problems

- Range from a *prolongation of PT* to *DIC*: may be due to sepsis or the effects of leukaemia itself, especially APL.

Priorities

- 1 Stabilize the patient.
- 2 Treat immediate problems, e.g. bleeding, sepsis.
- 3 Confirm diagnosis (morphology, cytogenetics, and flow cytometry).
- 4 Define the treatment strategy, often urgently.

Acute leukaemias: management

Stabilize the patient

- **Airway:** stridor may be secondary to mediastinal obstruction in certain cases of leukaemia, mainly T-ALL. If present, call the anaesthetist immediately and arrange transfer to ITU to start treatment.
- **Breathing:** breathlessness may be due to infection (including atypical organisms), leucostasis (high WCC), severe anaemia, cardiac failure (leucostasis, severe sepsis), and pulmonary haemorrhage. Give O_2 : where possible, use a pulse oximeter to monitor O_2 saturation, avoiding arterial puncture with thrombocytopenia. Leukapheresis may be indicated (consider if WBC >100 with AML, >50 with ALL).
- **Circulation:** shock is usually secondary to sepsis, but consider the possibility of blood loss if low platelets/clotting abnormalities or cardiac failure from leucostasis.
- Restore circulatory volume with crystalloid and blood components.
- Give broad-spectrum antibiotics immediately (after blood cultures) if sepsis suspected (➡ The febrile neutropenic patient 1, p. 648).
- Refer to a haematologist urgently.

Treat immediate problems

- **Infection:** until the blood film has been reviewed by a haematologist, assume the patient is neutropenic and treat all infections aggressively (➡ The febrile neutropenic patient 1, p. 648).
- **Bleeding:**
 - Transfuse cross-matched blood components. Caution if high WCCs.
 - If platelets $<10 \times 10^9/L$, give one pool of platelets. If there is active bleeding and platelet count $<50 \times 10^9/L$, give platelets.
 - If PT prolonged ($>1.5 \times$ control), give 4–5U of FFP.
 - If fibrinogen <1 – $1.2g/L$, consider cryoprecipitate in addition.

Transfusion in the presence of a high WCC is dangerous and can precipitate the complications of leucostasis.

- **High WCC:** discuss with haematologists. May require urgent leukapheresis, preferably in an ITU setting.

Confirmation of diagnosis

- Take a full history, looking for possible aetiological factors. Length of illness (was there a preceding chronic condition, e.g. ? myelodysplasia). Past medical history (? Down's syndrome, radiation/chemotherapy exposure). Occupation (? exposure to irradiation, benzenes, other mutagens). Family history (rare familial syndromes, e.g. Fanconi's anaemia).
- Examine the patient, looking for accessory clues to diagnosis (? lymphadenopathy in ALL, hepatosplenomegaly, gum hyperplasia in M5 monocytic leukaemias), splenomegaly in CML/non-Hodgkin's lymphoma (NHL)/myelofibrosis, and identifying potential sites for infection (dental caries, skin lesions, etc.)
- Final confirmation then rests upon a bone marrow aspirate, with samples being sent for morphology, chromosome analysis, and cell surface markers.

Acute leukaemias: treatment

The treatment of acute leukaemia depends upon the type of leukaemia and involves several courses of chemotherapy, taking months or even years to complete. The prognosis has improved in recent years and depends upon the exact diagnosis. Eighty per cent of children with ALL are now cured, whereas only around 30–50% of adults with AML are cured, depending on age. Most patients with APL survive long term if they do not succumb to acute bleeding. The impact of the diagnosis on often young patients and their families is devastating, and extensive time is needed in discussion; this should be done by a haematologist. Before embarking on chemotherapy, the following must be considered.

Sperm banking

Most forms of chemotherapy carry a risk of subsequent infertility. When desired by the patient, every attempt must be made to provide for banking of sperm collection prior to starting chemotherapy. Only 5–10% of men subsequently utilize their banked sperm for assisted fertility. Unfortunately, in practice, the presence of leukaemia itself often makes sperm non-viable, and the need to start treatment precludes repeated collections.

Discussion about side effects

Patients need to be warned about hair loss, sterility, emesis (less of a problem with current antiemetics but varies with individual), infections, bleeding, mucositis, secondary cancers, etc. Patient-orientated literature is available on acute leukaemia and chemotherapy, and may be helpful.

Other considerations

- LP (? CNS involvement). Indicated in:
 - ALL (because of high risk of CNS relapse).
 - AML if high WCC at presentation.
 - Any neurological symptoms/signs.
- Human leucocyte antigen (HLA) typing of patient/siblings may be considered, with a view to possible BMT in the future.
- CMV status should be determined, especially if BMT is an option, along with a viral screen, e.g. HIV, etc.

Prior to commencement of chemotherapy

- Commence allopurinol 24h in advance. Rasburicase is used if there is a high risk of tumour lysis syndrome (200 micrograms/kg IV od for 5–7 days); no G6PD.
- Prescribe regular antiseptic mouthwashes, to be used 4–5 times/day in conjunction with antimicrobial prophylaxis (oral fluconazole, ciprofloxacin, aciclovir).
- Ensure adequate hydration, aiming for 3L/day input.
- Give antiemetics before chemotherapy, and at regular intervals during treatment with chemotherapy. Appropriate regimens include:
 - Ondansetron 4–8mg IV/PO bd
 - Metoclopramide 10–20mg IV/PO plus dexamethasone 2–4mg IV/PO 4- to 8-hourly.

Early complications of bone marrow transplantation

Always urgently contact and refer the patient back to their BMT centre. Close contact with the ICU for supportive care.

Morbidity and mortality following BMT (especially allogeneic BMT) is high, particularly within the first 100 days. The patients are very reliant on close medical and nursing surveillance to ensure that they do not perish from preventable/treatable causes. Patients may occasionally present outside of their transplant unit overnight or at weekends. They will be vulnerable to infections—bacterial, viral, fungal, and protozoal. Even if the neutrophil count is normal, treat the patients as being neutropenic, as they will have poorly functioning lymphocytes and low antibody production. This section is a guide to some of the problems encountered.

Acute graft-versus-host disease

This causes skin rashes, either localized (e.g. to palms) or widespread. There may be upper and/or lower GI symptoms (severe watery diarrhoea) and liver dysfunction (deranged LFTs). Consider early treatment (usually high-dose methylprednisolone) for graft-versus-host disease (GVHD), with budesonide for diarrhoea. Always discuss with the transplant centre.

Fever

See ➔ The febrile neutropenic patient 1, p. 648.

Upper GI symptoms (mucositis, vomiting)

Symptomatic management, including adequate analgesia (e.g. opiates) and H₂-antagonists or PPIs. Search for an infectious cause (mouthwash and swabs for HSV and *Candida*). Antiemetics usually required: lorazepam 1–2mg q8–12h; metoclopramide 10–20mg q6–8h; or ondansetron 4–8mg q12h.

Diarrhoea

Rehydrate. Monitor strict fluid balance. Stool culture (green watery diarrhoea suggests GVHD). May require early biopsy and steroids if large-volume diarrhoea. Malabsorption is also a problem. Discuss with the transplant centre.

Abnormal LFTs (drugs, GVHD, veno-occlusive disease)

Supportive measures: monitor fluid balance, coagulation tests, renal function; adjust drug doses accordingly. Search for an infectious aetiology. Veno-occlusive disease presents as hepatomegaly, jaundice, and weight gain in the early post-transplant period. Liver USS with Doppler of the hepatic and portal veins (reversed hepatic portal flow seen in veno-occlusive disease). Discuss with the transplant centre.

Interstitial shadowing on CXR

These may be diffuse or localized and associated with varying degrees of fever, breathlessness, and hypoxia.

Causes

Pulmonary oedema [fluid overload, cardiac failure due to chemo-/radio-therapy, non-cardiac (ARDS)—related to sepsis or drug toxicity]; infection [bacterial, viral (especially CMV), fungal, *Pneumocystis*]; thromboembolic; GVHD; pulmonary haemorrhage; idiopathic.

Management

Supportive treatment: O₂, diuretics (if pulmonary oedema), and ventilatory support. CXR changes often minor if neutropenic, and so consider HRCT early. Cover for infectious causes with broad-spectrum antibiotics, antifungal agents, or occasionally antiviral agents (if viral respiratory tract infection is suspected). PCP is unusual if the patient is on co-trimoxazole prophylaxis. Consider bronchoscopy.

Early complications of BMT

- Skin rash.
- GI complications:
 - Nausea and vomiting.
 - Mucositis.
 - Diarrhoea.
- Abnormal LFTs.
- Haemorrhagic cystitis.
- Interstitial shadowing on CXR.
- Cardiovascular complications:
 - Cardiac failure.
 - Hypertension.
- Deteriorating renal function.
- CNS complications.
- Sepsis.
- Drug toxicity.

Complications of BMT

Cardiac failure

- Cardiac toxicity may be secondary to high-dose cyclophosphamide, total body irradiation, and/or previous anthracycline exposure.
- Transient ST- and T-wave abnormalities and LV dysfunction on Echo are seen in up to 30%, following conditioning prior to BMT.
- Overt cardiac failure may be seen with repeated high-dose steroid therapy that is required for episodes of GVHD.

Management

- Standard therapy with diuretics and ACEI.

Hypertension

- Very common in the early days post-BMT and due to ciclosporin therapy $\pm$ renal impairment.

Treatment

- Calcium antagonists [e.g. nifedipine slow release (SR) 10–20mg PO bd].

Deteriorating renal function

Causes

- Drug therapy (ciclosporin, amphotericin, aminoglycosides, chemotherapy, aciclovir, allopurinol).
- Pre-renal (dehydration, shock, bleeding).
- Tumour lysis syndrome (➡ Tumour lysis syndrome, p. 655).
- TTP (➡ Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, p. 654).

Haemorrhagic cystitis

Frequency, dysuria, and haematuria; commonly related to cyclophosphamide (caused by acrolein, a metabolite), but also seen with anthracyclines, cytosine arabinoside, etoposide, adenovirus, and BK virus infection. Prevent with mesna (see data sheet for dose).

Management

Supportive therapy with blood and platelet transfusion and hydration is usually sufficient. Discuss with urologists if severe, as more specialist intervention, such as bladder irrigation, may be required.

CNS complications

Symptoms

- May include seizures, drowsiness/confusion, focal neurological signs, stroke, and visual loss (cortical).

Causes

- Metabolic ($\downarrow$ Mg^{2+} , $\downarrow$ Ca^{2+} , hypoxia, liver failure, renal failure).
- Infection: bacterial, viral (e.g. HSV), fungal (especially *Aspergillus*), *Toxoplasma*, *Cryptococcus*.
- Drug toxicity; ciclosporin can cause tremor, confusion, and seizures.
- Intracranial haemorrhage.

- Cerebral infarction (embolic).
- Relapse of disease.
- TTP (➡ Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, p. 654).
- Steroid psychosis.
- PRES.

Investigations

- FBC and film, LDH, CT scan, LP (after correcting clotting and platelets), blood cultures, serology, Mg^{2+} and Ca^{2+} levels, Echo, drug level, chimerism studies, bone marrow assessment.

Management

- Specific therapy for the underlying cause.

The febrile neutropenic patient 1

- Neutropenia (in this context) may be defined as a total neutrophil count of $<1.5 \times 10^9/\text{L}$, regardless of total WCC.
- Significant infections are usually associated with a fever of $\geq 38^\circ\text{C}$. Severely ill patients and those on steroids may not be able to mount a fever; signs such as tachypnoea, tachycardia, or hypotension should be considered serious.
- The site of infection is not usually obvious; potential sites include the chest, Hickman line, or other central line (or inflammation around the exit site of the line), mouth, perianal area/perineum, urine, or skin.

Organisms

(See Box 10.5.)

- A microbiological diagnosis is reached in up to two-thirds of cases.
- Coagulase –ve staphylococci: Hickman or other IV lines.
- Viridans streptococci: mucositis $\pm$ previous exposure to quinolones.
- Fungal infections: occur after prolonged and profound neutropenia, previous antibiotic therapy, underlying lung disease (pulmonary aspergillosis), stem cell transplantation, or prolonged immunosuppression (steroids for >1 week).

Basic microbiological investigations

- *Blood cultures*: taken from Hickman line and by venepuncture. This allows line infections to be differentiated from bacteraemias.
- Culture of urine and faeces, including stool for *Clostridium difficile*. *C. difficile* toxin, adeno viral and rota viral antigens.
- *Cultures from other suspected sites*: e.g. line exit sites, sputum, skin lesions, throat. Consider TB cultures.
- *Viral serology*: less useful, as a rising titre is often necessary to diagnose infection. Viral detection (e.g. viral PCR-CMV, EBV and adenovirus PCR, respiratory viruses such as RSV, influenza, and parainfluenza), where possible, may be more helpful in an acute situation.
- *Line tips*: rush to the laboratory. Do not allow to dry out on the ward bench or insert into a throat swab medium.

Important points

- Antibiotic therapy should never be delayed to await further assessment of clinical progress or laboratory results.
- Neutropenic patients may not show a localized response to infection. The most common presentation is that of a fever of unknown origin.
- Pyrexia lasting $>48\text{h}$, despite IV antibiotics, usually requires some alteration to the antimicrobial regimen. Consider polymicrobial and/or fungal infection.
- *Platelet requirements increase with sepsis*: neutropenic patients are commonly also thrombocytopenic—keep platelet count above $20 \times 10^9/\text{L}$.
- Thrombocytopenia also demands care with invasive procedures. Central lines and urinary catheters should be inserted with platelet cover, and *arterial puncture is best avoided* (use pulse oximetry).

Box 10.5 Common and less common organisms in neutropenia**Common**

- Gram +ve (60%):
 - Coagulase –ve staphylococci—*Staphylococcus epidermidis*.
 - Streptococci—viridans streptococci.
 - Enterococci.
- Gram –ve (30%):
 - *Escherichia coli*.
 - *Klebsiella* spp.
 - *Pseudomonas aeruginosa*.

Other

- *Staphylococcus aureus*.
- *Corynebacterium* spp.
- *Acinetobacter* spp.
- Mixed infections.
- Anaerobes.
- *Stenotrophomonas* spp.
- Fungal infections:
 - *Candida* spp.
 - *Aspergillus fumigatus*.
- Viral infections (VZV, CMV):
 - *Pneumocystis jiroveci*.

The febrile neutropenic patient 2

Immediate management

Given the caveats described under ➡ The febrile neutropenic patient 1, p. 648, stabilization of a septic neutropenic patient is similar to that of any other septic patient.

- O₂, IV crystalloid, and vasopressors should be administered, as is appropriate to the patient's clinical condition.

Antimicrobial regimen

When in doubt, take haematological advice; use the hospital policy. Regimens for empirical therapy are based on broad-spectrum bactericidal antibiotics. Monotherapy is usually inappropriate, even when an organism has been isolated; the patient may well have >1 infection. A typical policy is shown in Table 10.11. See Box 10.6 for causes of failure to respond to empirical antibiotics.

Table 10.11 Empirical antibiotic therapy for febrile neutropenia

First line	• Piperacillin with tazobactam 4.5g IV tds (or meropenem 1g IV tds if penicillin-allergic or renal impairment) <i>plus</i> • Amikacin 15mg/kg IV od (guided by levels)
Second line	Add: • Vancomycin 1g IV bd (guided by levels) <i>or</i> • Teicoplanin 400mg IV od (bd for first 24h) if line infection is suspected
Third line	Consider AmBisome® 3–5mg/kg if fever not settling after 72h, especially in patients with long periods of neutropenia (e.g. AML or BMT patients). Discuss with the local haematologist. Urgent HRCT thorax

Notes

- Doses of *vancomycin* and *gentamicin* will need to be adjusted, according to serum levels.
- Add *metronidazole* 500mg IV q8h to first- or second-line regimens if fever persists and anaerobic infection possible (e.g. perineal sepsis or mucositis).
- Add *amphotericin*: most units use the lipid formulations Abelcet® or AmBisome® for proven (or possible) fungal infection. Voriconazole is used first line if *Aspergillus* is likely. Caspofungin or micafungin for *Candida*. Posaconazole is an oral alternative.
- The change from first- to second-line therapy should be considered under the following circumstances:
 - Persistent pyrexia >48h (or less if the patient's condition markedly deteriorates).
 - A new spike of temperature once the fever has settled on first-line antibiotics (suggesting emergence of another resistant organism).
 - Rising CRP in the face of apparently appropriate antibiotics.
- Choice of *third-line antibiotics* is often more arbitrary, and combinations should again be discussed with haematology and microbiology. Duration of neutropenia is an important factor, as fungal infections become more likely the longer the period of neutropenia.

Particular situations

- Infections of the mouth, perianal area, or elsewhere in the GIT: consider adding metronidazole for *Bacteroides* spp. and others.
- Suspected line infections: ensure good Gram +ve cover (vancomycin or teicoplanin). Consider linezolid if vancomycin-resistant enterococci (VRE) are present.
- Diarrhoea after prolonged antibiotic therapy: suspect *C. difficile*; consider empirical oral vancomycin and/or metronidazole, while awaiting stool toxin detection/culture results.
- Oropharyngeal mucositis due to reactivation of HSV is common. It is effectively prevented and treated with aciclovir; the main complication is bacterial super-infection.
- Pyrexia associated with a normal CRP virtually excludes bacterial or fungal infection as a cause of the fever.
- Deteriorating renal function: avoid nephrotoxic agents, particularly in combination (e.g. vancomycin, liposomal formulation of amphotericin, gentamicin).
- Systemic candidiasis may be manifest only as fever unresponsive to antibiotics: blood cultures are rarely positive; signs of local invasion (e.g. endophthalmitis) are seen in a minority. Have a high index of suspicion and treat aggressively with amphotericin or fluconazole. Hepatosplenic disease is often diagnosed with imaging.
- Invasive aspergillosis presents with fever, abnormal CXR/HRCT, and dyspnoea or sinusitis (invasive disease of the sinuses). There is extensive local tissue destruction with cavitating lung lesions or bone destruction of sinuses. Thoracic HRCT should be performed urgently. Treat aggressively with IV AmBisome® or voriconazole/micafungin/caspofungin/posaconazole.
- Granulocyte colony-stimulating factor (G-CSF) may shorten a period of neutropenia and may be used for certain patients. Discuss with haematology.

When selecting an antimicrobial regimen, it is worthwhile reviewing all recent microbiology results, including skin swabs (axilla, groin, perineal). Review past microbiology for resistant organisms that may need to be covered (e.g. MRSA, VRE, resistant *Pseudomonas*, *E. coli*, or *Klebsiella*).

Box 10.6 Causes of failure to respond to empirical antibiotics

- Wrong microbiological diagnosis: consider infection with fungi, viruses, protozoa, or mycobacteria.
- Polymicrobial infection.
- Line-associated fever.
- GVHD (also possible with liver transplantation).
- Drug fever.
- Inadequate antibiotic doses.
- Underlying disease (e.g. relapse).

Infections in the transplant patient

Infectious diseases are a major cause of mortality and morbidity following both solid organ and bone marrow transplantation, related to immunosuppression (and in the case of BMT, the innate immuno-incompetence in the neutropenic and early engraftment phases).

Different pathogens are typically implicated in infections, depending on the degree of immunocompetence of the patient:

- The neutropenic patient (➡ The febrile neutropenic patient 1, p. 648).
- The non-neutropenic transplant patient.

Cell-mediated immunity may be impaired for several months after bone marrow (and solid organ) transplantation. This predisposes to viral (CMV, HSV, adenovirus, EBV) and protozoal (*Pneumocystis jiroveci*, toxoplasmosis) infections.

- CMV infections: see ➡ Cytomegalovirus infections in transplant patients, p. 653.
- Suspected *Pneumocystis* pneumonia: treat with high-dose co-trimoxazole (0.96–1.44g q12h IV) and corticosteroids; consider urgent bronchoscopy/BAL if patient fit enough.
- Toxoplasmosis: usually due to reactivation of latent infection. Presents as intracranial SOL, meningoencephalitis, or diffuse encephalopathy. Seizures and focal neurological signs are common. Treatment is with pyrimethamine and sulfonamides. Give co-trimoxazole prophylaxis.
- Other viral infections:
 - HSV commonly produces localized infection and dissemination is rare, but recognized, to produce encephalitis and pneumonia. Treat with *high-dose aciclovir* IV.
 - VZV reactivation is frequently seen and most infections are mild; encephalitis and pneumonitis are usually fatal. Treat with *high-dose aciclovir* (10mg/kg IV q8h). Disseminated VZV can present as central abdominal pain, with little or no obvious rash.
 - Adenovirus infection produces interstitial pneumonitis, similar to CMV, and may disseminate.

Cytomegalovirus infections in transplant patients

(Also see Table 8.2.)

- May be acquired from the reactivation of previous CMV infection in the recipient, due to immunosuppression.
- May be acquired from the bone marrow from a CMV-positive donor or CMV-positive blood products (less likely due to universal leucodepletion. (*All BMT recipients should receive irradiated blood products.*)
- Occur more commonly in allogeneic and unrelated donor transplants, due to greater immunosuppression.

Presentation of acute CMV infections

- Fever of unknown origin.
- Positive CMV PCR (detected by routine blood testing).
- Graft failure/myelosuppression (anaemia, thrombocytopenia, leucopenia).
- Interstitial pneumonitis: deteriorating O₂ saturation, with widespread bilateral interstitial opacities on CXR.
- Enteritis (oesophagitis, gastritis, colitis): pyrexia, diarrhoea.
- Hepatitis.
- Retinitis.

Immediate management

- Ensure adequate respiration; consult the anaesthetist and consider CPAP/invasive ventilation early if O₂ requirements are increasing or the patient is becoming exhausted.
- Inform the haematologist responsible for the patient's care.
- Take blood for CMV PCR.
- If CMV is strongly suspected, commence ganciclovir/valganciclovir/foscarnet/cidofovir treatment immediately. Otherwise, consider:
 - Bronchoscopy/BAL if pulmonary infiltrate.
 - Upper or lower GI endoscopy and biopsy.

Treatment

- Valganciclovir 900mg bd or ganciclovir 5mg/kg bd should be commenced.
- Side effects include nephrotoxicity and myelosuppression/graft failure, which may be difficult to distinguish from the effects of CMV itself.

Hyperviscosity syndrome

Causes

Increased cellularity

- Polycythaemia (primary or secondary):
 - Haematocrit 50–60%.
- Leucocytosis (acute leukaemias):
 - WCC $>50\text{--}100 \times 10^9/\text{L}$.
 - CML ($>300 \times 10^9/\text{L}$).

Raised plasma proteins

- Waldenström's macroglobulinaemia:
 - IgM paraprotein level $>30\text{g/L}$.
- Myeloma, usually IgA subtype:
 - Paraprotein level $>80\text{g/L}$.

Presentation

Most patients develop symptoms when serum viscosity reached 5–6 centipoises (normal <1.8).

General features

- Muscle weakness.
- Lethargy, headache.
- Mental confusion, proceeding to coma.
- Visual disturbance.
- CCF.
- Fundoscopy:
 - Engorgement and sludging in the veins.
 - Haemorrhage, exudates.
 - Papilloedema.

Specific features

The predominant symptoms vary with the underlying cause.

- Raised paraprotein:
 - Bleeding/purpura: platelet dysfunction and factor deficiency.
 - Neuropathies.
 - Renal impairment.
 - Cardiac conduction abnormalities.
- Leucostasis:
 - Myocardial ischaemia/MI.
 - Pulmonary infiltrates.
- Polycythaemia:
 - Peripheral ischaemia.
 - TIAs/strokes.
 - MI.

Management

Arrange urgent intervention (same day), depending on the cause:

- Polycythaemia:
 - Venesect 1–2U.
 - Replace with normal saline.
- Leukaemia: leukapheresis or chemotherapy.
- High paraprotein: plasmapheresis.

Tumour lysis syndrome

A syndrome of metabolic abnormalities and renal impairment that can occur within hours or days of commencing chemotherapy, due to rapid lysis of tumour cells. It is most likely to occur with bulky, highly chemosensitive lymphoproliferative disease (e.g. T-ALL and Burkitt's lymphoma). Seen less commonly in other lymphomas, high-blast count leukaemias, and some germ cell tumours.

Features

- Uric acid ≥ 476 micromol/L or 25% increase from baseline $\pm$ urate nephropathy and oliguric renal failure.
- Hyperkalaemia (K^+ 6mmol/L or 25% increase from baseline), especially with progressive renal impairment.
- Hyperphosphataemia (≥ 1.45 mmol/L or 25% increase from baseline).
- Hypocalcaemia (≤ 1.75 mmol/L or 25% decrease from baseline) and hypomagnesaemia (due to rising PO_4^{3-}).
- Creatinine ≥ 1.5 times upper limit of normal (age >12 years or age-adjusted).
- Cardiac arrhythmias (secondary to $\uparrow K^+$, $\downarrow Ca^{2+}$, and $\downarrow Mg^{2+}$).
- Weakness, twitching, tetany (hypocalcaemia).
- Severe metabolic acidosis (renal failure).
- Seizures.
- Sudden death.

Prevention

- Start *allopurinol* 300mg od (or bd) 48h prior to chemotherapy if renal function is normal.
- Rasburicase should be considered for high-risk patients (non-G6PD-deficient), such as Burkitt's lymphoma, high WCC ALL, and patients with LDH >2 times normal. Standard dose is 0.2mg/kg IV od for 5–7 days. A starting dose of 3mg is often effective.
- *Hyperhydrate*: vigorous hydration is important, and a fluid load of 3L/m²/day should be given to those patients who can tolerate it. A urinary catheter should be used to monitor output.
- *Leukapheresis* if high peripheral blast count.
- Continue IV fluids during therapy, giving furosemide to maintain diuresis (>100 mL/m²/h).
- Urine alkalinization no longer recommended (with sodium bicarbonate to keep urinary pH >7.0).

Management

- Emergency treatment of hyperkalaemia.
- Exclude bilateral ureteric obstruction by US.
- Avoid Ca^{2+} supplements, except if there is neuromuscular irritability.
- Monitor U&Es, PO_4^{3-} , Ca^{2+} , and urate at least twice daily for the first few days of treatment.
- Strict fluid balance measurements, with a urinary catheter if necessary.
- Indications for haemodialysis/intensive care:
 - Rising K^+ , creatinine, or PO_4^{3-} in spite of measures discussed earlier.
 - Metabolic acidosis.
 - Fluid overload or oliguria in spite of diuretics.

Hypercalcaemia of malignancy

(See  Hypercalcaemia, pp. 572–4.)

- Urgent intervention required if $\text{Ca}^{2+} > 3\text{mmol/L}$.

NB True Ca^{2+} = measured Ca^{2+} + $[(40 - \text{albumin}) \times 0.02]$.

Causes

- Bony metastases: probable local cytokine effect.
- Myeloma: secretion of an osteoclast-activating factor.
- Secretion of PTHrP (non-small cell lung cancer).
- T-ALL; NHL.

Presentation

- Nausea, vomiting, drowsiness, confusion, nocturia, polyuria, bone and abdominal pains, constipation.

Management

- Hydration: 3–6L over 24h, continuing for 4–5 days. In the past, loop diuretics (e.g. furosemide) were given routinely once fluid repletion had been achieved, to further increase urinary Ca^{2+} excretion. This has fallen out of favour due to the availability of drugs, such as bisphosphonates, and the potential fluid and electrolyte complications resulting from excessive diuresis, such as hypokalaemia, hypomagnesaemia, and even volume depletion if the diuretic-induced losses are not replaced. However, patients who are unable to excrete the administered salt because of renal insufficiency are at risk of fluid overload and should receive furosemide.
- Following overnight hydration, recheck Ca^{2+} and albumin. If symptoms persist and/or Ca^{2+} remains $> 3\text{mmol/L}$, give pamidronate disodium IV—a maximum of 90mg over 4h. It can be given as an infusion of 60mg/h. Suspected or established renal failure—maximum rate 20mg/h. Pamidronate is well tolerated; however, there is a small incidence of transient fever and flu-like symptoms.
- For myeloma, consider prednisolone 30–60mg PO daily. Start chemotherapy if relapse.

Superior vena cava obstruction

Presentation

Awareness of fullness of the head and tightness of the collar, symptoms exacerbated by bending down, syncope, breathlessness, facial suffusion and oedema, engorgement of veins in the neck, arms, and upper thorax.

Causes

- Usually bronchogenic carcinoma ($\pm$ secondary thrombosis of the SVC).
- Other tumours, including lymphoma, more rarely.

Management

- FBC and film, U&Es, Ca^{2+} , albumin.
- CXR, Doppler USS of neck veins if diagnosis uncertain.
- Heparin, providing platelet count and clotting function are normal.
- Arrange urgent radiotherapy (within 24h).
- May require stenting.
- Avoid Pemberton's sign.

Massive mediastinal mass

Presentation

- Dry cough, stridor, and dyspnoea, especially on lying flat.

Causes

- ALL (especially T-ALL with high WCC).
- High-grade NHL.
- Hodgkin's disease.
- Germ cell tumour.

Management

Histological diagnosis (or cytological from pleural effusion if present):

- General anaesthetic carries considerable risk.
- Definitive treatment (radiotherapy or chemotherapy).
- Consider prednisolone 1mg/kg/day if urgent treatment is required.

Rheumatological emergencies

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Acute monoarthritis: presentation

An acute monoarthritis should always be treated as septic arthritis until proven otherwise. Failure to treat septic arthritis is negligent. If left untreated, joint destruction is fast—50% of cartilage proteoglycan is lost within 48h; bone loss is evident within 7 days; mortality of *Staphylococcus aureus* arthritis is 10%.

Presentation

- Hot, swollen, red joint.
- Joint line tenderness.
- Restricted range of movement.
- Systemic features of fever and malaise.

Assessment

Look for any risk factors for infection

- DM.
- Immunodeficiency state (inherent or iatrogenic).
- Underlying structural joint disease (e.g. RA, prosthesis, joint replacement).
- High-risk sexual activity, IV drug abuse (predisposes to sacroiliitis and acromioclavicular joint infection).
- TB needs to be considered in at-risk populations.

Ask for risk factors for gout

- Alcohol.
- High-purine diet (e.g. shellfish, meat).
- Drugs (e.g. thiazides, furosemide, pyrazinamide).
- High cell turnover states (e.g. lymphoma, polycythaemia, psoriasis).
- Tophi (at ears, elbows, Achilles tendon).

Examine for evidence for multisystem disease

- Rash.
- Ocular involvement.
- Oro-genital ulceration.
- GI symptoms.
- Renal involvement.
- Pulmonary manifestations.

Conditions that mimic monoarthritis

- Bone pain or fracture close to a joint.
- Tendinitis (especially at the wrist).
- Bursitis (commonly olecranon or pre-patellar bursae; no joint line tenderness).
- Neuropathic pain.
- Soft tissue pain.

See Box 11.1 for the differential diagnosis of monoarthritis.

Box 11.1 Differential diagnosis of monoarthritis**Traumatic**

- Traumatic synovitis.
- Haemarthroses:
 - Fracture.
 - Haemophilia.
 - Ruptured anterior cruciate ligament.

Non-traumatic**Infective**

- *Staphylococcus aureus*.
- *Neisseria gonococcus*.
- *Staphylococcus albus*.
- Streptococcal.
- Gram –ve rods.

Crystals

- Uric acid (gout).
- Calcium pyrophosphate (pseudogout) .
- Hydroxyapatite— usually a monoarthritis (shoulder) in elderly ♀.

Monoarticular presentation of

- RA.
- Seronegative arthritis [e.g. reactive (Reiter's), psoriasis].
- SLE (usually small joint polyarthritis).

Miscellaneous

- Pigmented villonodular synovitis.
- Osteosarcoma.

Practice points

- Always assume that a monoarthritis is due to sepsis until proven otherwise.
- Perform a septic screen, including knee joint aspirate, immediately in the emergency department, and antibiotics started thereafter. Never aspirate a prosthetic joint. This should be discussed with orthopaedics.

Acute monoarthritis: investigations

Synovial fluid analysis

Aspirate the joint to dryness (➡ Joint aspiration, p. 852) and send fluid for:

- **WBC:** fluid may be placed in an EDTA tube.
- **Microbiology:** fluid into a sterile container and ideally a sample into blood culture bottles and for AFB.
- **Polarized microscopy:** for crystals; fluid into a sterile container.

See Box 11.2 for indications for synovial fluid aspiration, and Box 11.3 for contraindications to joint aspiration.

Take blood for

- **Blood cultures.**
- **FBC:** WBC high in infection and crystal arthritis.
- **CRP/ESR:** elevated with an inflammatory arthritis. Elevated ESR and normal CRP suggest SLE.
- **U&Es, LFTs:** may be impaired with sepsis.
- **Glucose:** ? diabetic.
- **Uric acid:** ? gout. (NB Urate may be normal in acute gout.)
- **Clotting:** bleeding diathesis causing haemarthrosis.
- **Immunology:** rheumatoid factor (RhF), anti-CCP antibodies, ANA, anti-dsDNA, complement levels (? RA or SLE).

X-ray of joint

- To exclude fracture. Chondrocalcinosis suggests pseudogout. (But *not* helpful in the early diagnosis of septic arthritis, as the appearance may be unchanged for up to 2 weeks in infection.)

Sepsis screen

- Chest radiograph; urine cultures; consider cervical, rectal, and throat swabs.

Aspirate any cutaneous pustules for Gram stain in patients with suspected gonococcal infection.

Box 11.2 Indications for synovial fluid aspiration in casualty

- Suspected septic arthritis.
- Suspected crystal arthritis.
- Suspected haemarthrosis.
- Relief of symptoms by removal of effusion in degenerative arthritis.

Box 11.3 Contraindications to joint aspiration

- Overlying infection, i.e. cellulitis.
- Bleeding diathesis.
- Prosthetic joints (must be aspirated in theatre by orthopaedic surgeons).

Septic arthritis

The most common pathogen in the UK is *S. aureus* (70%). *Neisseria gonorrhoea* is a common cause in the young, sexually active population. Other important causes include *Streptococcus*. *Haemophilus influenzae* should be considered in children.

Management

(See Box 11.4.)

- Admit and inform the orthopaedic team.
- Aspirate the joint to dryness (see Boxes 11.2 and 11.3 for indications and contraindications for aspiration, respectively). Prosthetic joints should be aspirated by the orthopaedic team in theatre—liaise with them and consider early arthroscopy to facilitate effective joint washout, especially if inflammatory markers are slow to fall.
- Full septic screen.
- Strict rest for the joint (bed rest); no weight-bearing on infected joints.
- Analgesics (NSAIDs). Consider adding a PPI if history of dyspepsia.

Antibiotics

- Initially IV for 2 weeks, then PO for a further 4 weeks.
- Empirically start with flucloxacillin 1g q6h and benzylpenicillin 1.2g q4h. For penicillin allergy, use vancomycin and clindamycin. In young children, use cefotaxime to cover *H. influenzae*.

(NB Aminoglycosides are not effective in the acidic pH of an infected joint; erythromycin penetrates the synovial fluid poorly.)

- Review antibiotics when microbiology available.
- For gonococcal arthritis, treat with IV benzylpenicillin 1.2g q4h for 7 days and then PO amoxicillin 500mg tds for 10 days. Remember to trace and treat contacts (liaise with the GUM team).

Box 11.4 Management key points: septic arthritis

- Analgesics.
- Aspirate the joint to dryness and perform a full septic screen.
- Antibiotics (initial empirical treatment): IV flucloxacillin (1g qds) and benzylpenicillin (1.2g q4h). For penicillin allergy, use vancomycin and clindamycin.
- Review antibiotics when microbiology available.
- Liaise with the orthopaedic team.
- Strict rest and no weight-bearing on the affected joint.

Crystal arthropathy

Management

- May usually be managed as an outpatient (see Box 11.5).
- Bed rest.
- Analgesics: NSAIDs with PPI cover, e.g. naproxen 500mg bd. Use cautiously in the elderly, patients with peptic ulceration, or patients with asthma, cardiac failure, or renal or liver disease.
- Colchicine is a good alternative if NSAIDs are contraindicated. Give 500 micrograms every 4–6h, as tolerated, until pain settles. In renal impairment, reduce the dose to 500 micrograms every 12h and monitor renal function. *Rheumatology* consultation if symptoms fail to settle. Intra-articular steroid injections may be given in patients who cannot take NSAIDs or colchicine (e.g. those with renal failure) and only have one or two actively inflamed joints. The diagnosis of acute gout should be confirmed and septic arthritis must be excluded before giving steroids.
- Systemic steroids may be given in patients who cannot take NSAIDs or colchicine and in whom intra-articular steroid injection is not an option because of polyarticular disease. Oral prednisolone (20–30mg/day) may be given for 3–5 days and then tapered over 7–10 days. Rebound attacks may occur when steroids are withdrawn. IM steroids (e.g. 120mg IM depot methylprednisolone) may also be used as an alternative if infection has been excluded.
- Allopurinol is contraindicated during acute gout, as it can exacerbate the acute episode. However, once treatment with an antihyperuricaemic drug (allopurinol or probenecid) has been started, it should not be stopped during an acute attack.
- Allopurinol may be started for prophylaxis when the acute attack has settled if the patient has had >2 attacks of acute gout in 1 calendar year, if tophi are present, or in cases of erosions or urate nephropathy. Initiation of these drugs should be accompanied by either an NSAID or colchicine (0.5mg bd) for 3–6 months, while the allopurinol dose is being uptitrated to a target urate level of <0.35 mmol/L.

Box 11.5 Management key points: acute gouty arthritis

- May be managed as an outpatient.
- Analgesics: NSAIDs, e.g. naproxen 500mg bd.
- Colchicine if NSAIDs are contraindicated (500 micrograms every 4–6h, as tolerated).
- If symptoms fail to settle: intra-articular steroids may be given when only one or two joints are affected (septic arthritis must be excluded first) or IM steroid injection if polyarticular
- Oral prednisolone may be given in patients who cannot take NSAIDs or colchicine and have polyarticular disease (20–30mg/day for 3–5 days and then tapered over 7–10 days). Septic arthritis must be excluded first. IM steroids are an alternative, provided infection has been excluded.
- Do not start allopurinol during an acute attack or stop it if the patient is already on it.

Polyarthritis (≥ 5 joints)

Presentation

- Pain.
- Stiffness (especially early morning).
- Swelling.
- Loss of function.

Differential diagnosis

- RA.
- Seronegative arthritis:
 - Psoriatic arthropathy.
 - Reactive arthritis.
 - Ankylosing spondylitis.
 - Enteropathic arthritis.
- SLE.
- Crystal arthropathy:
 - Chondrocalcinosis.
 - Gout.
- Infections:
 - Viral.
 - Bacterial.

Miscellaneous

- Sarcoid: associated with erythema nodosum (20%) and transient RA like polyarthritis or acute monoarthritis.
- Behçet's syndrome: polyarthritis ($\pm$ erythema nodosum) with painful orogenital ulceration and iritis.
- Familial Mediterranean fever: occurs in Middle Eastern individuals with recurrent attacks of fever, arthritis (usually monoarticular), and abdominal or chest pain (serositis).
- Transient polyarthritis may be associated with SLE, bacterial endocarditis (➔ Infective endocarditis (IE), pp. 102–3), para-infectious, Reiter's, reactive arthritis, and Henoch–Schönlein purpura.

Investigations

- Aspirate a large affected joint and analyse the synovial fluid (➔ Joint aspiration, p. 852).
- Blood cultures if fever or raised CRP.
- FBC with differential count.
- CRP and ESR.
- Biochemical profile (U&Es, LFTs, urate) and glucose.
- Bone profile and PTH, RhF, anti-cyclic citrullinated peptide (CCP) antibodies (RA).
- ANA, anti-dsDNA, complement levels (SLE).
- Viral serology—HIV, EBV, CMV, parvovirus, hepatitis B and C.
- X-ray of the hands and feet (even if no foot symptoms) (may show chondrocalcinosis, typically knees and wrists, or changes of RA with periarticular osteoporosis or erosions).

Management

General measures

- NSAIDs, e.g. naproxen 500mg bd, adjusting the dose according to symptoms and response (caution in elderly patients, patients with dyspepsia, asthmatics, and patients on anticoagulants).
- IM methylprednisolone (120mg) or PO prednisolone (e.g 20mg prednisolone for 5 days) will settle most acute flares of RA/inflammatory arthritis. Exclude infection first.
- Consider specific treatment of the underlying condition.
- Consider the need for physiotherapy and exercise regimens to reduce long-term disability.

(See Table 11.1.)

Table 11.1 Disease associations of autoantibodies

Antibody	Association
RhF	RA and many disorders
Anti-CCP antibody	RA (more sensitive and specific than RhF)
ANA	SLE and many autoimmune disorders
Anti-dsDNA	SLE
ENA	ENA includes: • RNP • Ro (SSA) • La (SSB) • Anti-centromere • Scl-70 • Jo-1
Ribonucleic protein (RNP)	Mixed connective tissue disease (MCTD) SLE
Ro (SSA)	Primary Sjögren's, SLE
La (SSB)	Primary Sjögren's
Anti-Sm	SLE
Anti-centromere	Limited systemic sclerosis
Scl-70	Systemic sclerosis (diffuse)
Jo-1	Jo-1 syndrome—a subset of polymyositis, associated with interstitial lung disease
Anticardiolipin	SLE, antiphospholipid syndrome

Rheumatoid arthritis

Clinical features

- Typically young women (♀:♂—3:1).
- Symmetrical polyarthritis involving the small joints of the hands and feet.
- May present as relapsing or persistent monoarthritis.
- Signs most common in hands, feet, knees—but remember synovial joints of the spine (and atlantoaxial joint/ligaments) and larynx (arytenoid joints).
- Extra-articular manifestations: vasculitis, subcutaneous nodules, lymphadenopathy, peripheral neuropathy, anaemia (normochromic normocytic, iron deficiency, drug-induced aplasia, haemolytic), ocular involvement (e.g. scleritis), pleurisy, pericarditis, pulmonary fibrosis.

Management

- General measures as before (➡ Polyarthritis, pp. 666–7).
- Early, intensive disease-modifying anti-rheumatic drugs (DMARDs) reduce long-term joint damage. Most commonly methotrexate, but others such as hydroxychloroquine, sulfasalazine, and leflunomide. Some older patients may still be taking gold. Steroids are used as induction/bridging therapy, while DMARDs are established.
- Biological therapies are increasingly used, e.g. anti-cytokine therapies such as tumour necrosis factor (TNF)- α blockers (etanercept, adalimumab, and infliximab), B-cell depletion (rituximab), interleukin (IL)-6 receptor blockade (tocilizumab) and, more recently, small molecules, e.g. Janus kinase (JAK) inhibitors.
- Symptomatic treatment with NSAIDs.

Seronegative arthritides (spondyloarthropathies)

Psoriatic arthropathy

Clinical features

- May present as an asymmetrical large- or small-joint oligoarthritis, symmetrical polyarthritis, or a clinical picture similar to RA or ankylosing spondylitis. Joint destruction may be extensive (arthritis mutilans).
- Look for rash (knees, elbows, scalp, behind the ears, umbilicus, natal cleft) and nail changes (pitting, onycholysis, ridging).

Management

- Treatment is similar to that for RA, with DMARDs and biologics.
- Chloroquine and steroids may worsen psoriasis.

Reactive arthritis

Clinical features

- Typically young, sexually active individual with oro-genital ulcers (painless), conjunctivitis (which may progress to iritis), and rash (soles of feet—keratoderma blenorrhagica).
- May occur following non-specific urethritis or gastrointestinal infection, e.g. with *Shigella*, *Salmonella*, *Yersinia*, or *Campylobacter*.

Treatment

- NSAIDs are the main therapy and treat underlying infection.
- GUM review.

See Box 11.1 for Reiter's syndrome.

Practice points

Marked morning joint pain or stiffness is most likely to be due to inflammatory arthritis.

Reactive arthritis

Clinical features

- Comprises a triad of seronegative arthritis, non-specific urethritis, and conjunctivitis.
- Skin lesions are psoriasiform (keratoderma blenorrhagicum) with brown macules and pustules on the soles and palms.
- Arthritis usually begins ~2 weeks after infection, and the lower limb joints are most commonly affected (asymmetrical) and resolves over months.
- It may be associated with a sterile urethral discharge and mild dysuria. Erosive lesions may affect the penis (circinate balanitis) or mouth.
- Rarely progresses to give aortic incompetence, heart block, and pericarditis.

Treatment

NSAIDs, and sometimes steroids, are the mainstay of therapy.

Ankylosing spondylitis

Clinical features

- Enquire about axial skeleton involvement (lower lumbar back pain, with early morning stiffness, that improves with exercise).
- Peripheral joint involvement, uveitis, and anaemia of chronic disease may be found.

Management

- NSAIDs for pain.
- Physiotherapy to try to prevent progressive immobility.
- Anti-TNF therapy or anti-IL17 (secukinumab) may be used for axial disease.
- If there is peripheral arthritis—sulfasalazine or methotrexate.
- Refer to a rheumatologist for long-term management.

Enteropathic arthritis

- Large-joint arthritis often coincides with active IBD, but not always.
- Arthritis may predate the onset of intestinal symptoms; often there are other extraintestinal manifestations (e.g. erythema nodosum and iritis).
- Treatment of colitis usually improves arthritic symptoms.

Infections

- *Viral*: rubella, parvovirus B19 (common, often presents with a generalized rash), and HIV seroconversion.
- *Bacterial*: *Gonococcus* (rash, tenosynovitis, sexually active), *Staphylococcus* (immunosuppressed, with septicaemia and seeding to several joints), IE (vasculitic lesions, heart murmur).
- *Treatment*: see ➡ Infectious diseases, pp. 469–503.

Vasculitis

The term vasculitis denotes an inflammatory reaction with destructive changes of blood vessel walls. Vasculitides are classified into *primary* and *secondary* (see Box 11.6) types.

Classification

(See Table 11.2.)

Table 11.2 Primary systemic vasculitis (simplistic classification)

	Primary	Secondary
Large arteries	Giant cell arteritis, Takayasu's arteritis	Aortitis secondary to RA or syphilis
Medium arteries	PAN, Kawasaki	Infection, e.g. HBV
Small and medium arteries	EGPA (Churg–Strauss) and GPA (Wegener's granulomatosis), microscopic polyangiitis	Vasculitis secondary to RA, SLE, systemic sclerosis, drugs, or HIV
Small vessel	Henoch–Schönlein purpura, hypersensitivity vasculitis	Drugs, HCV or HBV infection

Box 11.6 Causes of secondary vasculitis

- IE.
- Malignancy.
- RA.
- SLE.
- Cryoglobulinaemia (strongly associated with hepatitis C).
- Drug reaction.

Organ involvement varies with the type of vasculitis but commonly includes the skin, joints, kidneys, lungs, and the nervous system.

Presentation

- Arthralgia or arthritis, myalgia.
- PUO.
- Generalized systemic illness, e.g. weight loss, malaise.
- Rashes: splinter haemorrhages, nail fold infarcts, purpura, livedo reticularis, nodules.
- Renal disease: haematuria, proteinuria, hypertension, renal failure (see Box 11.7).
- Lung disease: haemoptysis, cough, breathlessness, pulmonary infiltrates (see Box 11.7).
- Neurological disease: mononeuritis multiplex, sensorimotor polyneuropathy, confusion, seizures, hemiplegia, acute cerebral syndrome.

See Box 11.8 for patterns of ANCA.

Box 11.7 Vasculitides affecting lungs or kidneys

Causes of lung haemorrhage and renal failure

- Goodpasture's syndrome.
- GPA (formerly WG).
- Microscopic polyarteritis.
- SLE.
- Leptospirosis.

Causes of renal failure only (no lung haemorrhage)

- Anti-GBM disease.
- Small-vessel vasculitis.
- Secondary vasculitis.
- Medium-vessel vasculitis (rare).

Box 11.8 Patterns of ANCA

c-ANCA (anti-neutrophil α -proteinase 3—PR3)

- GPA (formerly WG).
- Microscopic polyangiitis.

p-ANCA (anti-myeloperoxidase or elastase—MPO)

- Microscopic polyangiitis.
- EGPA (formerly Churg–Strauss syndrome).

Atypical ANCA

- UC (also p- or x-ANCA).
- Sclerosing cholangitis.

ANCA tests need to be interpreted in the clinical context. ANCA tests are seen in infection, malignancy, and a wide range of connective tissue disorders. A negative ANCA does not exclude any of the above.

Systemic lupus erythematosus

Assessment

This is a chronic autoimmune disorder characterized by the production of a wide range of autoantibodies against both intracellular and cell surface antigens, though most often with ANA. It commonly affects young women (1:3000 in the UK) and is ten times more common in West Indian black patients.

Patients with SLE may present to A&E in one of two ways:

- 1 Known diagnosis of lupus having become acutely unwell. Clinically, one has to determine whether their symptoms reflect disease activity, an underlying infection due to iatrogenic/inherent immunocompromise which may precipitate a flare of the disease, or an unrelated condition.
- 2 As a presenting diagnosis; the attending physician should be alert to the varied presentations of lupus.

Clinical features

- *Constitutional (90%)*: fever, malaise, weight loss.
- *Musculoskeletal (90%)*: arthralgia, myalgia, myositis, correctable deforming arthropathy (Jaccoud's) secondary to ligament and capsular laxity, avascular secondary to steroid therapy.
- *Cutaneous (80–90%)*: butterfly rash, photosensitive rash, discoid lupus, Raynaud's phenomenon, purpura, scarring alopecia, livedo reticularis, urticaria.
- *Haematological (75%)*: thrombocytopenia, anaemia (normochromic normocytic, Coombs +ve in 15%), leucopenia, and lymphopenia.
- *Neuropsychiatric (55%)*: depression, psychosis, fits, hemiplegia, cranial nerve lesions, ataxia, chorea, aseptic meningitis/encephalitis.
- *Renal (50%)*: glomerulonephritis, nephritis or nephrotic syndrome, proteinuria, hypertension.
- *Cardiovascular or respiratory (40%)*: pleurisy, pericarditis, pleural or pericardial effusion, Libman–Sacks endocarditis, shrinking lung syndrome.
- *Aphthous ulcers (40%)*.

Urgent investigations

- *FBC*: anaemia, thrombocytopenia, or leucopenia (especially lymphopenia).
- *U&Es, creatinine*: renal failure.
- *ESR*: elevated with disease activity.
- *CRP*: typically normal; if raised, suggests infection.
- *APTT*: prolonged if there is lupus anticoagulant or 'anticardiolipin' antibody (IgG or IgM), anti- β 2-glycoprotein-1 antibody or lupus anticoagulant.
- *Blood cultures*: infection-induced flare-ups.
- *Urine*: dipstick for proteinuria or haematuria, microscopy for casts, culture for infection.
- *CXR*: infection or pleurisy.
- *ABG*: hypoxia with infection or PE.

Practice points

SLE is often characterized by a high ESR and a normal CRP.

A raised CRP in SLE should make you think of infection, infection, infection!

Other investigations

- *Immunology*: ANA, anti-dsDNA, ENA, anticardiolipin, anti- β 2-glycoprotein-1 antibody, lupus anticoagulant, complement levels.
- *LFTs*: usually normal.
- *Viral*: consider PCR for CMV.
- *Urine*: urine protein:creatinine ratio.

Points to note

- Immunology:
 - >95% are ANA +ve (dsDNA antibody is almost pathognomonic of SLE).
 - Anti-dsDNA antibody titre may correlate with disease activity.
 - Low complement levels correlate with disease activity (and renal involvement).
 - 40% are RhF-positive.
- Pneumococcal and meningococcal infections are more common in patients with SLE as a consequence of either hereditary or acquired deficiencies of components of the complement pathway.
- Immunosuppressive therapy renders patients susceptible to the usual range of opportunistic infections, including *Pneumocystis*, CMV, and mycobacteria.
- Chest and urine are the most common sources of infection in clinical practice.
- Disease activity classically shows an elevated ESR, but a normal CRP.

An elevated CRP should alert you to look for an underlying infection.

Management

- Exclude infection.
- *Prednisolone* 20–30mg od.
- Additional *immunosuppressive therapy*, such as pulsed methylprednisolone, or cyclophosphamide, should be given on consultation with a rheumatologist.
- *Antibiotics* if infection is suspected.
- *Hydroxychloroquine* (200mg/day) may be added, especially if there is cutaneous or joint involvement.

Granulomatosis with polyangiitis and microscopic polyarteritis nodosa 1

- Both of these small-vessel vasculitides may present to casualty with AKI (rapidly progressive glomerulonephritis).
- GPA (formerly known as WG) classically involves the upper and lower respiratory tracts and the kidneys.

Clinical features

- *Systemic features*: fever, malaise, weight loss.
- *Upper respiratory*: nasal discharge, nosebleeds, sinusitis, collapse of the nasal bridge, deafness (all suggest a diagnosis of PGA).
- *Lower respiratory*: shortness of breath, haemoptysis, cavitating lung lesions.
- *Kidneys*: nephritis with deranged renal function, haematuria, proteinuria, active urinary sediment.
- *Musculoskeletal*: myalgia, arthralgias.
- *Neurological*: both peripheral and central.

Urgent investigations

- *FBG*: anaemia, neutrophil leucocytosis, thrombocytosis. Raised eosinophil count suggests EGPA (formerly known as Churg–Strauss syndrome).
- *Renal function*: impaired renal function or AKI.
- *LFTs*: low albumin (nephrotic syndrome). Elevated AST, ALT, and ALP with hepatitis.
- *CK and AST*: may be elevated due to myositis.
- *PT and APTT*: prolonged with widespread vasculitis and DIC.
- *ESR and CRP*: elevated.
- *Blood cultures*: sepsis.
- *ABG*: hypoxia (haemorrhage or infection), metabolic acidosis (renal failure).
- *Urine*: dipstick for blood or protein, microscopy and culture, urine protein:creatinine ratio.
- *Sputum*: culture (infection).
- *Ca²⁺/PO₄³⁻*: low corrected Ca²⁺ and high PO₄³⁻ suggest chronicity.
- *CXR*: shadowing seen in lung haemorrhage or infection; cavitating lesions typically occur in GPA.
- *USS of the kidneys*: if in renal failure, to exclude obstruction and needed prior to renal biopsy.

Granulomatosis with polyangiitis and microscopic PAN 2

Immunology

- *c*-ANCA: positive (see ➡ Points to note, p. 679).
- ANA, *anti*-dsDNA: to exclude SLE.
- *RhF*.
- *Complement levels*.
- *Anti-GBM antibody*: a positive test suggests anti-GBM disease, such as Goodpasture's syndrome, in which there is rapid progressive glomerulonephritis and lung haemorrhage.
- *Cryoglobulins*: to exclude as a cause of vasculitis.
- *Hepatitis serology*: hepatitis B and C.

Miscellaneous investigations

- *ECG*: baseline changes of hyperkalaemia if AKI is present.
- *Lung function tests*: measurement of KCO (high with lung haemorrhage).
- *Echo*?: indolent IE (as a cause of vasculitis).
- *CT sinuses*: commonly involved in GPA.
- *Renal biopsy*: histological diagnosis [light/immunofluorescence/electron microscopy (EM)].

Management

- Involve specialists early—rheumatology and renal.

Emergency management

- Patients commonly die from hypoxia (pulmonary haemorrhage, pulmonary oedema), arrhythmias (due to electrolyte abnormalities), and concomitant infection.
- Ensure adequate *oxygenation*, and consider ventilation if necessary.
- Assess *fluid balance*, and monitor urine output carefully.
- Consider *invasive haemodynamic monitoring* (CVP, arterial line, Swan–Ganz catheter).
- Patients with nephritis may be volume-overloaded with *pulmonary oedema*. Treat with IV furosemide (80–120mg; high doses may be required), GTN infusion, venesection, or haemodialysis or haemofiltration.
- *Correct electrolyte abnormalities*: hyperkalaemia (➡ Acute kidney injury: management, pp. 298–9).
- Consider urgent haemodialysis or haemofiltration in patients with AKI or hyperkalaemia (consult renal physicians).
- Treat precipitating infections empirically with *broad-spectrum antibiotics* until a pathogen is identified.
- Treat the underlying vasculitis:
 - High-dose prednisolone (e.g. 60mg/day or IV methylprednisolone).
 - Cyclophosphamide (only after renal or rheumatological opinion).
 - Plasmapheresis (renal units).

Points to note

- The ANCA test provides a rapid screening test and shows high sensitivity for patients with small-vessel vasculitis.
- Patients with GPA are classically c-ANCA positive (cytoplasmic pattern of immunofluorescence, antibody against elastase I), while patients with microscopic polyangiitis may be either p-ANCA (perinuclear pattern of immunofluorescence, antibody against myeloperoxidase) or c-ANCA positive. A negative ANCA does not, however, preclude the diagnosis of a small-vessel vasculitis.
- Underlying infection, especially IE and chronic meningococcaemia, should always enter the differential diagnosis of a patient with small-vessel vasculitis.
- An infectious episode, such as an URTI, often will precipitate the presentation of a small-vessel vasculitis.

Cryoglobulinaemia

Cryoglobulins are Igs that precipitate at low temperatures and dissolve on rewarming. They precipitate in the superficial capillaries or outside vessels in the coldest part of the skin to produce microinfarcts or purpura. Cryoglobulinaemia occurs in several conditions.

- Essential cryoglobulinaemia implies the absence of an identifiable cause.
- Renal disease is associated with all three types and is thought to involve immune complex pathways.
- Mean age: 42–59 years; ♂:♀, 2:3.

Type 1 monoclonal

- Type 1 cryoglobulinaemia, or simple cryoglobulinaemia, is the result of a monoclonal Ig, usually IgM or IgG.
- Associated with myelo- or lymphoproliferative disease.
- Heavy proteinuria, haematuria, and renal failure may occur (MPGN).
- Serum C4 and C1q are low.

Type 2 (mixed monoclonal) and type 3 (mixed polyclonal)

- Type 2 and type 3 cryoglobulinaemia (mixed cryoglobulinaemia) contain RhFs (often IgM). These RhFs form complexes with the fragment, the crystallizable (Fc) portion of polyclonal IgG. The actual RhF may be monoclonal (in type 2 cryoglobulinaemia) or polyclonal (in type 3 cryoglobulinaemia) Ig.
- Type 2 is associated with immune complex vasculitis, and 50% have evidence of renal disease. Many cases are associated with HCV infection.
- Type 3 mixed polyclonal is associated with SLE and systemic infections (post-streptococcal nephritis, leprosy, and syphilis). Renal involvement is also seen.

Clinical features

- Renal involvement (haematuria, proteinuria, renal failure).
- Raynaud's phenomenon.
- Purpura (especially legs).
- Arthralgia and fever.
- Confusion and weakness (secondary to hyperviscosity).
- Hepatosplenomegaly (probably a manifestation of the underlying aetiology).

Management

- Treat the underlying cause (e.g. hepatitis C or haematological malignancy).
- There is no specific treatment.
- Plasmapheresis and immunosuppressive therapy may be tried.

Giant cell arteritis (temporal arteritis)

- The most common type of large-vessel vasculitis in clinical practice, with an incidence of 1:10 000. This is typically a disorder of the elderly (mean age 70 years, with a ♀:♂ ratio of 2:1).
- The diagnosis is made clinically (see Box 11.9) and is supported by an elevated acute phase response (ESR, CRP, and thrombocytosis) and temporal artery histology.
- The classical pathological description is of a segmental granulomatous pan-arteritis, but in the early stage, changes may be confined to thickening of the internal elastic lamina, associated with a mononuclear cell infiltrate.

Investigations

- *FBC*: normochromic anaemia, thrombocytosis.
- *Biochemistry*: elevated ALP.
- *ESR*: >50mm in the first hour, 95% of cases.
- *CRP*: elevated.
- *CXR*: exclude underlying bronchial carcinoma.
- *Urinalysis*: exclude haematuria and proteinuria.
- *Temporal artery biopsy*.

Management

- Patients with suspected giant cell arteritis should be started on *high-dose prednisolone immediately*, as delay may result in blindness, and a temporal artery biopsy should be arranged within 1 week of starting steroids, to secure a diagnosis and confidently commit the patient to steroids for 1–2 years.
- If there are no visual symptoms, jaw claudication, or features of large vessel vasculitis, give 40mg of prednisolone.
- If there are visual symptoms or jaw claudication give 60mg of prednisolone. If potentially reversible symptoms persist or worsen, the dose may be ↑ until symptomatic control is achieved.
Suggested tapering regimen:
 - continue with 40–60mg prednisolone until symptoms and laboratory abnormalities resolve (at least 3–4 weeks);
 - reduce dose by 10mg every 2 weeks to 20mg;
 - then reduce by 2.5mg every 2–4 weeks to 10mg; and
 - then reduce by 1mg every 1–2 months provided there is no relapse.
 Check Hb and ESR/CRP prior to each reduction in the steroid dose.
- If visual loss is strongly suspected to be due to giant cell arteritis: IV pulsed methylprednisolone (1g for 3 days) may be given, followed by prednisolone 1mg/kg PO per day (maximum of 60mg/day), as recommended above.
- Large-vessel giant cell arteritis should be suspected in patients with prominent systemic symptoms, limb claudication, or persistently high inflammatory markers despite adequate glucocorticosteroid therapy. Imaging techniques, such as PET and MRI scanning, should be reserved for the assessment of suspected large-vessel involvement.
- Jaw claudication is a strong predictor of visual loss.

- Low-dose aspirin (plus PPI for gastroprotection) is recommended to reduce the risk of visual loss, TIAs, or stroke.
- Because the patient may be on steroids for 1–2 years, consider osteoporosis prophylaxis—encourage adequate dietary Ca^{2+} and vitamin D intake. Bisphosphonates for either prophylaxis or treatment may also be appropriate.
- All patients should ideally have a temporal artery biopsy performed to try to confirm the diagnosis. A normal biopsy does not exclude the diagnosis because of the ‘skip’ nature of the disease.

Box 11.9 Clinical features of giant cell arteritis

• Headache	90%.
• Temporal artery tenderness	85%.
• Scalp tenderness	75%.
• Jaw claudication	70%.
• Thickened/nodular temporal artery	35%.
• Pulseless temporal artery	40%.
• Visual symptoms (including blindness)	40%.
• Polymyalgic symptoms	40% (↻ Polymyalgia rheumatica, p. 684).
• Systemic features	40%.
• CVA or MI	rare.

Further reading

Dasgupta B, Borg FA, Hassan N, et al. BSR and BHPR guidelines for the management of giant cell arteritis. *Rheumatology* 2010;**49**(8):1594–7. <https://doi.org/10.1093/rheumatology/keq039a>

Polymyalgia rheumatica

PMR is a clinical syndrome characterized by an acute phase response (high ESR or high CRP), which predominantly affects the elderly Caucasian population, with a median age of onset of 70 years and an annual incidence of ~1:2500.

Clinical features

- Proximal muscle stiffness and pain without weakness or wasting (see Box 11.10).
- Systemic symptoms of malaise, fever, and weight loss.

Box 11.10 Causes of proximal upper and lower girdle stiffness or pain

- *Cervical spondylosis ± adhesive capsulitis*: no acute phase response, CK (normal).
- *Lumbar spondylosis*.
- *Osteomalacia*.
- *Fibromyalgia*.
- *Hypothyroidism*: no acute phase response, ↑ CK.
- *Polymyositis/dermatomyositis*: ↑ acute phase response, ↑ CK.
- *Inflammatory arthritis*: ↑ acute phase response.

Investigations

- *FBC*: normochromic normocytic anaemia.
- *U&Es, LFTs*: elevated ALP is common (50%).
- *CK*: normal (if high, consider myositis or hypothyroidism).
- *ESR*: high (>40mm/h initially).
- *CRP*: high.
- *RhF and anti-CCP antibodies*: PMR may be the presenting feature of RA.
- *CXR*: PMR symptoms may be the presenting feature of a neoplasm.

Treatment

- *Steroids*: prednisolone 15mg PO od initially, reducing to 5–10mg od over 2–3 months and very slow reduction thereafter. Some patients may require treatment for years. Consider bone prophylaxis.
- Monitor response with symptoms and ESR.

Points to note

- PMR and giant cell arteritis form part of a clinical spectrum of disease, and up to 40% of patients with biopsy-proven giant cell arteritis have polymyalgic symptoms.
- Polymyalgic symptoms may be the presenting feature of an underlying neoplasm or connective tissue disease.
- Polymyalgic symptoms should respond dramatically to prednisolone within 7–10 days. Failure to respond should alert the clinician to the possibility of an underlying neoplasm or connective tissue disease.

Practice points

- Never diagnose PMR in a patient <50 years old.
- Always consider paraneoplasia in PMR.
- Obtain a temporal artery biopsy ASAP after starting steroids for giant cell arteritis.

Back pain

~5% of all medical consultations in the UK are for back or neck pain. In the majority of patients, no definite anatomical diagnosis is made (non-specific back pain), but it is important not to miss the sinister causes of back pain (see Boxes 11.11 and 11.12).

Box 11.11 Causes of back pain

Mechanical back pain

- Spondylolisthesis.
- Spondylosis.
- Intervertebral disc prolapse.
- Spinal stenosis (claudication-type pain).
- Apophyseal joint disease (exacerbated by lumbar extension, cervical or thoracic rotation).
- Non-specific back pain.
- Trauma.

Inflammatory back pain

- RA.
- Seronegative spondyloarthritides:
 - Psoriatic.
 - Ankylosing spondylitis.
 - Reiter's.
 - Enteropathic.

Referred pain

- Aortic aneurysm.
- Pyelonephritis, renal calculus.
- Pancreatitis.

Box 11.12 Causes of 'sinister' back pain

- Infection (discitis/epidural abscess).
- Malignancy.
- Myeloma.
- Osteoporotic crush fracture.
- Paget's disease.

History

Is the pain likely to be mechanical, inflammatory, or sinister in origin?

- Mechanical back pain is exacerbated by prolonged sitting or standing and can be precipitated by trauma.
- Inflammatory back pain is characterized by prolonged early morning stiffness and is relieved by exercise.
- Sinister back pain (e.g. malignancy and infection) often leads to pain at night, constant pain, and local bony tenderness, and may be accompanied by other systemic symptoms.
- Are there any sensory or motor symptoms? Ask specifically for any change in bowel or bladder function.

Practice points

- Back pain at night suggests a sinister cause such as cancer or infection.
- Patients with acute onset of back pain and signs suggestive of a high lesion (e.g. L1–L3/4) may have weak thighs and absent knee jerks, and are unlikely to have a disc lesion and may have a tumour.

Examination

- General: look for evidence of malignancy.
- Spine (palpation for tenderness; muscle spasm; cervical spine flexion, extension, rotation, and lateral flexion; thoracic spine rotation; lumbar spine flexion, extension, and side flexion; compression of sacroiliac joints).
- Neurological examination looking specifically for absent ankle jerks (slipped disc) or long-tract signs in the legs. S1 nerve root signs and symptoms can be produced by a lesion in the region of the upper lumbar cord (central disc prolapse compressing the S1 nerve root).
- Always do a rectal examination and test perineal sensation.

Investigations

Patients with back pain occurring at night and patients with neurological signs warrant investigation.

- X-rays of spine and CXR (? malignancy).
- FBC and ESR (elevated with sinister causes of pain).
- Biochemical profile (Ca^{2+} , ALP, and PO_4^{3-}).
- Igs and protein electrophoresis (? myeloma).
- PSA.
- Bence-Jones protein.

Further imaging

- CT or MRI scan (superior to CT for imaging the spinal cord and roots).
- Technetium bone scan for 'hot spots' (neoplastic or inflammatory).

Management

- Analgesics.
- Bed rest.
- Physiotherapy.
- Appropriate referral to a specialist.

Prolapsed intervertebral disc

Acute postero-lateral herniation of a lumbar disc, usually L4–L5 or L5–S1, is a common cause of acute incapacitating lower back pain. There is often a clear precipitating event (e.g. lifting), and pain may radiate in the distribution of the L5 or S1 nerve root.

Patients should be examined carefully for:

- Paraspinal muscle spasm which is often prominent.
- Straight leg raising which is typically reduced on the affected side.
- Nerve root signs, and test sacral and perineal sensation; always do a rectal examination.
- L5 lesion which leads to weakness of the extensor hallucis longus, ankle dorsiflexion, and ankle eversion; and altered sensation which is perceived in the L5 dermatome.
- S1 lesion which leads to weakness of ankle plantar flexion, ankle eversion, and a diminished or lost ankle jerk; and altered sensation which is perceived in the S1 dermatome.
- Neurosurgical emergencies (see Box 11.13).

Treatment

- If the X-rays reveal a fracture, refer the patient to the orthopaedic team; severe pain from inflammatory arthritides should be referred to the rheumatologists.
- The majority of patients respond to conservative management.
- Rest until the acute pain subsides, followed by mobilization and physiotherapy (patients may often be managed at home, with instructions to return to the GP or doctor for review in 2–3 weeks).
- Non-steroidal anti-inflammatory agents.
- Physiotherapy.

Box 11.13 Neurosurgical emergencies presenting as back pain

An acute disc prolapse at the L2/3 level may cause bilateral multiple root lesions and may affect bladder and bowel function (cauda equina syndrome).

This requires immediate investigation:

- Acute cauda equina compression (➡ Spinal cord compression: assessment, p. 448).
- Acute cord compression (➡ Spinal cord compression: assessment, p. 448).

C₁-esterase inhibitor deficiency (angioneurotic oedema)

This condition may be inherited or acquired, occurring in ~1:50 000 in the UK.

Hereditary

- Autosomal dominant inheritance.
- Usually presents in the second decade.
- Characterized by low serum concentrations of complement components C2, C4, and C₁-inhibitor, but normal C1 and C3 levels; therefore, if you send for C3 and C4, the C4 will be low but C3 will be normal.

Acquired

- Paraneoplastic syndrome: autoantibody against C₁-esterase inhibitor.
- Characterized by low serum concentrations of complement components C1, C2, and C4.

Clinical features

- Laryngeal oedema (48% of attacks); may be life-threatening.
- Subcutaneous oedema (91% of attacks) affecting the face, buttocks, genitals, and limbs. Usually non-itchy.
- Abdominal symptoms: pain, vomiting, and diarrhoea.

Precipitating factors include

- Stress.
- Infection.
- Pre-menstrual.
- Oestrogen-containing contraceptive pill.
- ACEIs.

Management

Acute severe attack

- C₁-esterase inhibitor plasma concentrate (an IVI of 1000–1500U), usually effective in 30–60min.
- FFP 2–4U may be given if C₁-esterase inhibitor plasma concentrate is not available.

Laryngeal oedema

- If a patient is admitted with laryngeal oedema, 60% O₂ should be given immediately; blood gases should be checked, and a senior anaesthetist called as intubation or tracheostomy may be required.
- IM adrenaline 0.5–1mL, 1:1000 (⊕ Anaphylaxis, p. 342).
- Hydrocortisone 200mg IV.
- Chlorphenamine 10mg IV may be administered initially prior to the infusion of C₁-esterase inhibitor.

Prophylaxis

Those with >1 attack per month:

- Tranexamic acid (1–1.5g 2–4 times daily); effective in 28%.
- Attenuated androgens, e.g. danazol (unlicensed indication).

Dermatological emergencies

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Stevens–Johnson syndrome and toxic
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Erythroderma 702

Generalized pustular psoriasis 704

Autoimmune bullous disease 706

Herpes zoster 709

Eczema herpeticum 709

Cutaneous drug reactions

Presentation

Cutaneous drug reactions usually develop 1–2 weeks following initiation of a medication; however, some severe adverse reactions may present later (e.g. 4–6 weeks) after treatment initiation.

- **Exanthematous/Morbilliform drug eruption:** ~50% of cutaneous drug reactions. Generalized and symmetrical maculopapular erythema $\pm$ scaling and pruritus (see Fig. 12.1). Absence of systemic symptoms/signs. Resolves rapidly when drug is stopped. May require symptomatic treatment.
- **Urticaria:** ~25% of drug reactions. Sudden onset of intensely pruritic erythematous/oedematous skin lesions that resolve within 24h. May be associated with *angio-oedema* where there is deeper tissue oedema that can involve mucous membranes. May also be associated with life-threatening *anaphylaxis* in which oropharyngeal irritation, bronchospasm, hypotension, and tachycardia can be seen (➡ Anaphylaxis, p. 342). Most cases due to an IgE-mediated allergic reaction; however, certain drugs (e.g. opiates and radiocontrast media) can act directly on mast cells to liberate histamine or lead to $\uparrow$ leukotrienes (e.g. NSAIDs). Urticarial eruptions due to serum sickness may persist and have associated systemic symptoms.
- **Fixed drug eruption:** isolated, well-demarcated erythematous lesions, often on the extremities, face, or genitalia that can be painful/blister. Rechallenge may cause recurrent lesions at the same site. Common drugs include sulfonamides, tetracyclines, barbiturates, and NSAIDs.
- **Photosensitive drug eruptions:** cutaneous reaction limited to sun-exposed sites. May be due to either a phototoxic reaction (non-immune, e.g. tetracyclines, NSAIDs, and fluoroquinolones) or a photoallergic reaction (immune-mediated, e.g. thiazide diuretics and sulfonamides). Some drugs cause photosensitive porphyria cutanea tarda or photo-onycholysis.
- **Erythema multiforme (EM):** rapid onset of erythematous lesions with a typical 'target' appearance (see Fig. 12.2), often affecting the extremities or the face. Severe 'EM major' variant involves mucous membranes. EM more commonly has an infectious aetiology but may be triggered by certain medications.
- **Acute generalized exanthematous pustulosis (AGEP):** rapid onset of widespread sterile pustules, often starting in skin creases. Associated with fever and leucocytosis. More rapid onset than generalized pustular psoriasis (➡ Generalized pustular psoriasis, pp. 704–5).
- **Drug reaction with eosinophilia and systemic symptoms (DRESS):** presents as an exanthematous drug eruption, but associated with fever and systemic symptoms, which commonly include facial oedema, lymphadenopathy, and drug-induced hepatitis. Common drugs include anticonvulsants, sulfonamides, and allopurinol. Associated with ~10% mortality.
- **Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN):** life-threatening immune-mediated epidermal necrolysis, triggered by drug hypersensitivity (➡ Stevens–Johnson syndrome and toxic epidermal

necrolysis, pp. 698–700). Disease spectrum defined by the extent of body surface area involved (SJS <10%; SJS–TEN overlap 10–30%; TEN >30%). Mucosal involvement in both. Reported due to wide range of drugs, but mostly frequently sulfonamides, anticonvulsants, and antiretrovirals.

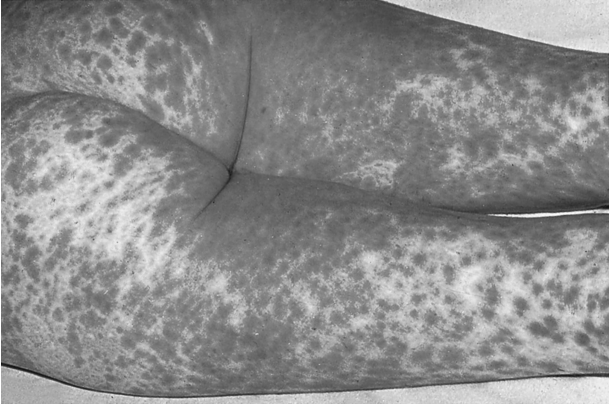


Fig. 12.1 Morbilliform eruption caused by administration of ampicillin to a patient with infectious mononucleosis.

Reproduced from MacKie R. *Clinical Dermatology*, 2003, with permission from Oxford University Press.



Fig. 12.2 Erythema multiforme on the leg; note the presence of target lesions.

Reproduced from MacKie R. *Clinical Dermatology*, 2003, with permission from Oxford University Press.

Points to note

- The 'severe cutaneous adverse reactions' (SCAR) refer to AGEP, DRESS, SJS, and TEN. These are often grouped together, as they are associated with systemic involvement, hospitalization, and high morbidity/mortality.
- Peripheral drug eosinophilia is seen in certain drug reactions, such as DRESS, but is uncommon across all cutaneous drug reactions.
- Parenteral drug administration is more commonly associated with anaphylaxis.
- Cutaneous drug reactions are more common in patients with HIV.

Management

(See Box 12.1.)

- Severe angio-oedema and anaphylaxis require immediate treatment (➡ Anaphylaxis, p. 342).
- Stop any responsible drugs, and prescribe an alternative if necessary. Hospitalized patients receiving numerous drugs should be assessed carefully, and all non-essential therapy discontinued.
- Most cutaneous drug reactions rapidly resolve on discontinuing the causative medication. Symptoms can be alleviated and resolution expedited with sedating/non-sedating antihistamines, a medium-potency topical steroid, and frequent applications of emollients.
- If SCAR is considered, specialist advice should be sought urgently. The patient will require assessment for systemic involvement, including general examination and blood tests (FBC, U&Es, and LFTs), and may require hospitalization. Oral steroids (prednisolone 0.5–1mg/kg/day) may be required for EM, AGEP, or DRESS but should be given only under specialist supervision. The management of SJS/TEN is considered separately (➡ Stevens–Johnson syndrome and toxic epidermal necrolysis, pp. 698–700).
- Pyrexia may occur with cutaneous drug reactions, but an underlying infection should be excluded.

Box 12.1 Management key points: cutaneous drug reactions

- Consider the primary lesion type and distribution and if there is any mucosal involvement.
- Document all recent medications and the chronological association with onset of rash/symptoms.
- Assess for associated signs, e.g. fever or lymphadenopathy.
- If concern of systemic involvement, perform blood tests, including FBC, U&Es, and LFTs.
- Discontinue the causative medication, and consider oral antihistamine, medium-potency topical steroid, and emollient.
- If SCAR is considered, seek urgent specialist advice.
- Severe angio-oedema and anaphylaxis require immediate treatment (➡ Anaphylaxis, p. 342).

- Persistent reactions, despite withdrawal of medication(s), raise the possibility of other causes to rash or SCAR.
- Although a rechallenge (oral/topical) with a suspected drug may provide a definitive diagnosis, subsequent reactions may be more severe. If fixed drug eruption is considered, patch testing may aid the diagnosis. If IgE-mediated hypersensitivity is considered, the patient should be referred to an allergist for assessment.
- Skin biopsy may aid in the diagnosis of certain drug reactions such as fixed drug eruptions, EM, and AGEP; however, the diagnosis is often clinical.

Urticaria and angio-oedema

Presentation

- *Urticaria* presents with sudden-onset intensely pruritic, oedematous skin lesions ('wheals'), with surrounding erythema ('flare'), that may coalesce to form larger plaques. Usually resolves within 24h to leave normal skin. New lesions may develop repeatedly.
- *Angio-oedema* presents with sudden-onset tissue swelling (deep dermis/subcutis oedema) that may be itchy/painful. Can involve mucous membranes, leading to upper respiratory tract obstruction.
- In severe urticaria/angio-oedema, systemic symptoms may predominate, with the development of *anaphylaxis* characterized by shock and collapse (➡ Anaphylaxis, p. 342). Features include bronchospasm, hypotension, and tachycardia.
- Urticaria/angio-oedema are divided between acute (<6wk history) and chronic (>6wk history) presentations.

Causes

Triggers of acute urticaria/angio-oedema are also common causes of anaphylaxis.

Acute

- Environmental allergens, e.g. nuts, shellfish, pollens, dust mite.
- Drugs, e.g. antibiotics (e.g. penicillins), NSAIDs, opiates, contrast media.
- Bee/wasp stings.
- Idiopathic.

Chronic

- Idiopathic.
- Physical causes, e.g. dermographism, cold/heat contact, delayed pressure, vibration, and sunlight exposure.
- Others, e.g. cholinergic (heat/exercise), contact, aquagenic.
- Conditions associated with urticaria, e.g. urticarial vasculitis, autoimmune disorders (e.g. SLE), and acquired/hereditary C_1 -esterase inhibitor deficiency (angio-oedema only).

Diagnostic points

- Acute urticaria/angio-oedema are most commonly triggered by environmental (either allergens or drugs) exposure, which should be elicited in the history, or can be idiopathic.
- Dermographism is the most common form of physical urticaria; briskly stroking the skin with a firm object induces linear wheals.
- Contact urticaria usually occurs within minutes after direct contact with various agents such as plants, aeroallergens, foods (such as cheese, eggs, fish), or latex. Contact sensitivity to latex products has a high incidence of anaphylaxis.
- Urticarial lesions that persist for >24h and leave darkened patches (bruise-like) may indicate urticarial vasculitis. Seek specialist advice, as should be confirmed with vasculitic screen and skin biopsy.

Management

- Anaphylactic reactions require immediate treatment (➡ Anaphylaxis, p. 342).
 - Lay the patient flat.
 - Secure the airway and give O_2 .
 - Establish cardiac/pulse oximetry monitoring.
 - Give IM adrenaline 0.5mg (0.5mL of 1:1000 adrenaline injection), and repeat every 5min according to BP, pulse, and respiratory function. IV adrenaline may be required if the patient is severely ill with poor circulation (➡ Anaphylaxis, p. 342).
 - Establish IV access (large-bore), and start IV fluids if hypotensive.
 - Give IV hydrocortisone 100–300mg and IV chlorphenamine 10–20mg. Continue H_1 -antagonist (e.g. oral chlorphenamine 4mg every 4–6h) for at least 24–48h, and continue if urticaria and pruritus persist.
 - If the patient deteriorates, start IV aminophylline infusion (see Box 2.6). Patients on β -blockers may not respond to adrenaline injection and may require IV salbutamol infusion.
- Acute urticaria $\pm$ angio-oedema is usually not life-threatening, unless associated with anaphylaxis or upper airway obstruction. If airway obstruction, treat as anaphylaxis and get urgent specialist advice for airway management. Otherwise:
 - Give oral antihistamines such as hydroxyzine 25mg or chlorphenamine 4mg.
 - A single dose of oral prednisolone (0.5–1mg/kg) may be given but should not be continued without specialist advice.
 - When the patient's condition has stabilized, discharge on regular maintenance treatment with oral non-sedating antihistamine (nsAH) (e.g. cetirizine 10mg/24h, levocetirizine 5mg/24h, desloratadine 5mg/24h, or fexofenadine 180mg/24h).
- Consider referral to a specialist for assessment (prick test) of IgE-mediated hypersensitivity or if no clear trigger for acute urticaria/angio-oedema established. Patch tests are not usually indicated in urticaria/angio-oedema.
- Patients with contact sensitivity to latex should use alternatives such as vinyl gloves. Such individuals should be warned to use only non-latex polyurethane condoms.
- Chronic idiopathic urticaria/angio-oedema can often be managed with long-term maintenance nsAH therapy. Treatment-resistant chronic urticaria should be referred for specialist advice, to evaluate for other causes and to guide management. Future treatment may include high-dose/combination nsAH, leukotriene antagonists, or systemic immunosuppressants, e.g. omalizumab (anti-IgE monoclonal antibody).

Stevens–Johnson syndrome and toxic epidermal necrolysis

Presentation

Acute onset of widespread epidermal blistering (necrolysis) with mucosal involvement, often preceded a few days by prodromal fever, malaise, and upper respiratory tract discomfort. Rash may initially mimic an exanthematous drug reaction but then rapidly progresses to purpuric macules, atypical target lesions, and confluent necrolysis.

Diagnostic points

- SJS and TEN represent the same condition within a severity spectrum, defined by the extent of body surface area involved (SJS <10%; SJS–TEN overlap 10–30%; TEN >30%).
- Necrolysis describes epidermal separation that results in loss of irregular epidermal sheets, rather like a large burn. It should be distinguished from discrete intact blisters characteristic of autoimmune bullous diseases.
- Epidermal detachment can be provoked with gentle lateral pressure (Nikolsky sign)—a useful test, although not specific, of SJS/TEN.
- Involves mucous membranes (i.e. oral, ocular, GI, and urogenital)—the extent of which must be assessed. Can also involve the respiratory tract.
- Differential diagnosis of SJS/TEN includes EM major, autoimmune blistering diseases, bullous lupus erythematosus, AGEF, and staphylococcal scalded skin syndrome (SSSS). In SSSS, there is loss of just the superficial epidermis in response to staphylococcal toxins, which is more common in children.
- Skin biopsy for histological assessment, with negative direct immunofluorescence, can support the diagnosis of SJS/TEN and aid the exclusion of other blistering skin conditions.

Causes

- Drug-induced—antibiotics (commonly sulfonamides), anticonvulsants, antiretroviral therapy (commonly nevirapine), certain NSAIDs, allopurinol, and sulfasalazine.
- SJS can be secondary to certain infections (e.g. *Mycoplasma*), although rare.

Adverse prognostic factors

- Age >40 years.
- Malignancy.
- Tachycardia >120bpm.
- Epidermal detachment >10% of body surface area.
- Blood urea >10mmol/L.
- Serum glucose >14mmol/L.
- Serum bicarbonate <20mmol/L.

Using these clinical parameters, mortality can be predicted using the SCORTEN prognostic index,¹ ranging from 0 (1% mortality) to 7 points (99% mortality).

Management

(See Box 12.2.)

The priorities are:

- 1 To identify and discontinue the causative drug.
- 2 To get specialist advice and multidisciplinary assessment/care.
- 3 Supportive care.
- 4 Screening for, and treatment of, sepsis.
- 5 To limit future complications.

Identify the cause

- Document a thorough drug history from the patient (and/or relatives), including over-the-counter and traditional/herbal medicines and previous adverse reactions to medications. Document the chronological association with the onset of symptoms (prodrome/rash).
- SJS/TEN usually develops 7–21 days after first administration of the culprit drug, or within 48h if previously sensitized to the drug.
- Identify the causative agent and discontinue. If the patient is receiving multiple drugs, stop all non-essential therapy.

Supportive care

Patients with SJS/TEN should be cared for by a multidisciplinary and multi-professional team led by clinicians with experience in cutaneous medicine and skin failure.

- Patients with significant epidermal loss (>10%) should be admitted to an intensive care setting (ICU or burns unit) where they should be barrier-nursed on a pressure-relieving mattress in a warm side room, with regular monitoring of core temperature.
- *Skin care:*
 - Patients should be handled carefully, and unnecessary adhesive monitoring devices avoided.
 - Greasy emollients should be applied every 4–6h to the skin, such as 50% white soft paraffin/50% liquid paraffin ('50/50') or aerosolized emollients, followed by a non-adherent absorbent dressing.
 - Detached epidermis should not be debrided/removed. Where the dermis is exposed, non-adhesive silicone dressings should be applied.
 - The skin can be cleaned daily with antiseptic products (e.g. chlorhexidine).
- *Pain control:*
 - Pain control should be frequently assessed and managed with regular paracetamol and opiate analgesics, as required.
 - Additional pain relief (e.g. short-acting opiate or Entonox®) may be required before dressing changes.
- *Eye care:*
 - The eyes should be assessed by an ophthalmologist and monitored daily.
 - Lubricant eye drops should be applied every 2h, and good eye hygiene maintained to prevent conjunctival adhesions.

- *GI care:*
 - Oral mucosal surfaces should be cleaned every 4–6h with an antiseptic (e.g. chlorhexidine) and an anti-inflammatory (e.g. benzydamine).
 - If there is extensive oral mucositis that limits food intake, nutritional intake should be supported via NG feeding.
 - Nasopharyngeal involvement may result in airway obstruction and necessitate ventilation.
 - Prophylactic H_2 -antagonist or PPI should be given to limit the risk of gastritis/ulceration.
- *Urogenital care:*
 - Catheterization should be considered if there is dysuria or obstruction, to aid fluid management and limit stricture formation.
 - Urogenital skin and mucosa should be regularly assessed.
- Fluid balance should be monitored closely, as there will be high insensible losses. If possible, fluids should be administered PO or via an NG tube. Avoid IV lines to reduce the risk of sepsis.
- Daily blood tests, including FBC, U&Es, LFTs, and glucose (hyperglycaemia can cause an osmotic diuresis, increasing fluid loss).
- Prophylactic anticoagulation with LMWH, if not contraindicated.

Preventing infection

- SJS/TEN patients should be barrier-nursed in a side room.
- IV lines should be removed as soon as possible to reduce infection risk.
- Multiple skin sites, mucosal sites, sputum, and urine should be cultured at least every 48h.
- Prophylactic antibiotics are only indicated if the risk of sepsis is extremely high such as severe neutropenia or a heavy single-strain bacterial colonization of the skin. Prophylactic topical antibiotics (e.g. skin/eyes) are generally not recommended.
- If febrile, blood cultures should be taken daily; however, fever is a common feature of TEN and does not always indicate an infection.
- Antibiotics should be started if there is positive blood, urine, or sputum culture or indirect evidence of sepsis such as hypothermia, hypotension, fever, decreasing level of consciousness, or reduced urinary output.

Specific systemic therapy

- Systemic treatments that have been used in SJS/TEN include corticosteroids, ciclosporin, and IVIG; however, there is no clear consensus from published studies that any of these improve outcome. Further controlled trials are required to establish the role of these treatments in SJS/TEN. Therefore, these treatments should only be started following specialist advice, as local guidelines may vary.

The British Association of Dermatologists have published guidelines on the management of SJS/TEN.²

Box 12.2 Management key points: SJS/TEN

- SJS and TEN represent the same condition within a severity spectrum.
- Patients with SJS/TEN should be cared for by a multi-professional team led by clinicians with experience in cutaneous medicine and skin failure.
- Identify the causative drug and discontinue. If the patient is receiving multiple medications, stop all non-essential therapy.
- If >10% of the body surface area is involved, consider admission to an intensive care setting (ICU or burns unit).
- Barrier-nurse in a warm side room on a pressure-relieving mattress, and monitor the core body temperature.
- Instigate a multidisciplinary team to advise on supportive care for the skin, eyes, GIT, and urogenital tract.
- Emollients (e.g. '50/50') every 4–6h.
- Monitor fluid balance, FBC, U&Es, and LFTs closely.
- Consider catheterization.
- Encourage a high-calorie diet and protein supplements. NG feeding may be required.
- Ensure adequate pain control, including analgesic mouthwashes.
- Lubricant eye drops every 2h.
- At least every 48h screen for cutaneous, mucosal, sputum, and urine bacterial colonization/infection. Have a low threshold for antibiotic therapy when indicated.

References

1. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol* 2000;**115**:149–53.
2. Creamer D, Walsh SA, Dziewulski P, et al. U.K. guidelines for the management of Stevens–Johnson syndrome/toxic epidermal necrolysis in adults 2016. *Br J Dermatol* 2016;**174**:1194–227.

Erythroderma

Presentation

- Exfoliative dermatitis affecting >90% of the body surface area. Can be acute or chronic in presentation, with acute erythroderma more likely to present as an emergency.
- Associated scale can be fine (pityriasiform) or coarse (psoriasiform).
- Itch is common.
- Patients may be febrile or hypothermic because of loss of temperature control mechanisms.
- Chronic erythroderma may be associated with nail dystrophy, diffuse hair loss, and ectropion. Palmo-plantar hyperkeratosis and peripheral lymphadenopathy may be prominent.

Causes

Erythroderma can be the clinical presentation of a wide range of different conditions:

- *Common:* dermatitis (atopic, contact, or seborrhoeic), psoriasis, drug reaction, or idiopathic.
- *Rare:* cutaneous T-cell lymphoma, pityriasis rubra pilaris, autoimmune bullous diseases, toxic shock syndrome, or paraneoplastic rash.

Investigations

- Monitor FBC, U&Es, albumin, Ca^{2+} , and LFTs regularly.
- Blood cultures and skin swabs. Sustained pyrexia, hypotension, or clinical deterioration should prompt a search for underlying sepsis.
- Skin biopsy should be performed, as histological features of the underlying causative condition are often present.
- Indirect immunofluorescence of blood serum and/or direct immunofluorescence of the skin biopsy should be performed in case of autoimmune bullous disease.

Management

(See Box 12.3.)

General measures

- Discontinue all unnecessary medications.
- Nurse in a warm room, with regular monitoring of the core temperature and fluid balance. Patients should be nursed on a pressure-relieving mattress.
- Encourage oral fluids, a high-calorie diet, and protein supplements. NG feeding may be required. Avoid IV cannulae, as they can be a source of infection.
- Monitor fluid balance closely: daily weights and clinical examination (as allowed by the exfoliation). Catheterize, if necessary, for fluid management.

Specific therapy

Liaise with a specialist early, as establishing a diagnosis will guide subsequent management.

- Skin should be treated every 4–6h with greasy emollients such as 50% white soft paraffin/50% liquid paraffin ('50/50').
- Wash with water and emollient soap substitutes.
- Oral sedating antihistamines such as hydroxyzine (25–100mg/24h in divided doses) may be beneficial, with the dose adjusted according to severity and weight.
- Application of topical steroids may be beneficial but should be initiated only under specialist supervision.
- Depending on the underlying cause, early systemic treatment may be required. For example, in erythrodermic atopic dermatitis, oral corticosteroids may be indicated, whereas in erythrodermic psoriasis, ciclosporin or a biologic medication may be indicated. Therefore, specialist advice must be sought prior to initiating systemic treatment.

Complications

- Hypothermia.
- Infection.
- Hypoalbuminaemia.
- High-output cardiac failure.

Box 12.3 Management key points: erythroderma

- Discontinue all unnecessary medications.
- Nurse in a warm room and on a pressure-relieving mattress.
- Monitor the core temperature and fluid balance closely.
- Fluids: encourage oral fluids.
- Feeding: encourage a high-calorie diet and protein supplements. NG feeding may be required.
- Emollients (e.g. '50/50') every 4–6h.
- Oral sedating antihistamines, e.g. hydroxyzine.
- Topical steroids/systemic therapy: liaise with a specialist early.

Practice points

Most cases of erythroderma are due to an underlying skin condition or a drug reaction. Therefore, take a careful history to establish any prior skin disease(s), recent new medications, or dose changes.

Generalized pustular psoriasis

Presentation

- Rapid onset of widespread erythema and superficial pustules, usually in a patient with a history of plaque psoriasis. Pustules are often at the periphery of annular patches of erythema and may become confluent.
- Can be a rebound phenomenon triggered by rapid tapering/withdrawal of systemic corticosteroids in patients with plaque psoriasis. Localized pustular psoriasis can also be triggered by topical irritants (e.g. vitamin D analogues).
- Can present rarely in people with no prior history of plaque psoriasis, and a similar presentation can occur in pregnancy.
- Widespread disease (von Zumbusch-type), associated with pyrexia and systemic symptoms such as malaise, anorexia, and arthralgia.
- Differential diagnosis includes subcorneal pustular dermatosis, AGEP, and generalized HSV infection.

Natural history

- There are repeated acute episodes of generalized pustulation, associated with pyrexia and systemic symptoms. Pustules resolve in 5–7 days and produce extensive superficial crusting but then rapidly recur.
- Patients with widespread disease can develop secondary septicaemia or ARDS.
- Elderly patients have a worse prognosis.

Investigations

- Monitor FBC, U&Es, and LFTs regularly. A neutrophil leucocytosis is common. Can be associated with hypocalcaemia.
- Bacterial or viral infection should be excluded by appropriate swabs and culture/PCR. Pustules should be sterile. If febrile, take blood cultures.
- Perform ABGs if the patient is hypoxic or an abnormal CXR.

Management

(See Box 12.4.)

Liaise with specialists at an early opportunity.

- Enforce bed rest; monitor the temperature and fluid balance closely.
- Oral fluids, with a high-calorie diet and protein supplements.

Topical therapy

- Treat the skin every 4–6h with a greasy emollient, e.g. 50% white soft paraffin/50% liquid paraffin ('50/50').
- Bathe daily with emollients and antiseptic washes.
- Extensive crusting and exudation can be treated with topical potassium permanganate soaks.
- Avoid topical treatments (e.g. corticosteroids, vitamin D analogues, coal tar, and dithranol), unless under specialist supervision, as may cause severe irritation and exacerbation of the rash.

Systemic therapy

- Systemic treatment may be required for long-term disease control (e.g. ciclosporin or biologics) but should only be started under specialist supervision.
- Bacterial infection should be treated with appropriate antibiotics.

Box 12.4 Management key points: generalized pustular psoriasis

- Nurse with bed rest on a pressure-relieving mattress.
- Monitor fluid balance, FBC, U&Es, and LFTs closely.
- Emollients (e.g. '50/50') every 4–6h.
- Encourage a high-calorie diet and protein supplements.
- May require systemic treatment under specialist supervision.

Autoimmune bullous disease

Presentation

- Range of conditions that lead to sudden-onset fluid-filled blisters (see Fig. 12.2).
- Often itchy and may be preceded by a 'pre-bullous' rash such as urticated erythematous plaques in bullous pemphigoid (see Fig. 12.3).
- Can involve mucous membranes.

Causes

- *Common*: bullous pemphigoid (see Box 12.5).
- *Rare*: pemphigus vulgaris (see Box 12.5), dermatitis herpetiformis, pemphigus foliaceus, paraneoplastic pemphigus, pemphigoid gestationis (second/third trimester), bullous lupus erythematosus, linear IgA disease, and epidermolysis bullosa acquisita.

Poor prognostic features

- Pemphigus (higher mortality than other bullous diseases).
- Older age.
- Extensive involvement.

Diagnosis

- Skin biopsy at the edge of a fresh blister for histology and direct immunofluorescence studies.
- Blood serum for indirect immunofluorescence studies.

Management

Liaise with a specialist at an early opportunity. Management differs for each autoimmune bullous disease; therefore, it is important to rapidly establish a diagnosis.

General measures

- Intact blisters should be aspirated, where possible, and not de-roofed (i.e. the epidermis should be left in place). Examine for new blisters daily.
- If there is extensive blistering, greasy emollients should be applied frequently and a chlorhexidine bath additive used for washing. Diluted potassium permanganate soaks can be applied to weeping areas.
- Avoid adhesive dressings.
- Give oral nsAH (e.g. hydroxyzine) for pruritus.
- Monitor fluid balance carefully and FBC, U&Es, and LFTs.

Specific systemic therapy

Liaise with a specialist:

- *Bullous pemphigoid*: localized/mild disease may respond to super-potent topical steroids alone (e.g. clobetasol) and/or oral tetracyclines (e.g. doxycycline 200mg/day). Extensive disease will require systemic immunosuppression (e.g. prednisolone 0.5–1mg/kg/day), with the dose



Fig. 12.3 Blisters of bullous pemphigoid. Large, tense, raised lesions are seen on an erythematous eczematized base.

Reproduced from MacKie R. *Clinical Dermatology*, 2003, with permission from Oxford University Press.

gradually reduced according to clinical response. Caution in patients with coexisting psoriasis vulgaris, as psoriasis may flare/pustulate with subsequent corticosteroid withdrawal.

- *Pemphigus vulgaris*: requires systemic immunosuppression (e.g. prednisolone 1mg/kg/day).
- Steroid-sparing agents, such as azathioprine or mycophenolate mofetil, are often used for the long-term management of bullous pemphigoid or pemphigus vulgaris once initial disease control has been achieved. Refractory disease may need to be treated with second-line agents, such as cyclophosphamide or rituximab (anti-CD20 mAb).
- Oral mucosal lesions may require additional regular antiseptic and anti-inflammatory mouthwashes, with good analgesia.
- If evidence of conjunctival disease, liaise with the ophthalmologist early.
- If the condition deteriorates, consider secondary bacterial or viral infection.

Box 12.5 Bullous pemphigoid vs pemphigus vulgaris

Bullous pemphigoid is characterized by sub-epidermal blisters, as the target antigen is at the dermal–epidermal junction. Clinically, this presents as tense, fluid-filled blisters. Insect bites and thermal burns also lead to sub-epidermal blisters, hence their similar appearance. Lesions most commonly affect the limbs and trunk, and mucosal involvement is rare. Bullous pemphigoid is more common in elderly patients.

Pemphigus vulgaris is characterized by intra-epidermal blister formation. The resultant blisters are flaccid and often present as ruptured erosions. Lesions most commonly affect the trunk and oral mucosa.

Herpes zoster

See ➡ Herpes zoster (shingles), p. 484.

Eczema herpeticum

Presentation

- Sudden onset of widespread umbilicated vesiculo-pustular lesions, which are painful. Lesions progress to haemorrhagic crusts and leave monomorphic punched-out erosions.
- Most common in patients with pre-existing atopic eczema but can occur in other pre-existing skin conditions, e.g. ichthyosis vulgaris and mycosis fungoides.
- Due to cutaneous HSV infection and may occur following a primary episode of herpes labialis or after contact with an infected individual.
- Patients usually pyrexial and tachycardic; however, cardiorespiratory collapse unusual.
- Lesions may also have a golden crust, as secondary staphylococcal infection ('impetiginization') is common.

Management

- Early specialist advice is required, as patients may require hospitalization. Can progress rapidly, so localized disease should be treated aggressively.
- Assess carefully for involvement of the ocular branch of the trigeminal nerve if facial rash (i.e. associated involvement of the nose). If concern of ocular involvement, liaise with the ophthalmologist urgently.
- Start high-dose IV aciclovir at the earliest opportunity (up to 10mg/kg 8-hourly in the immunocompromised). If IV therapy not possible, give valaciclovir 500mg PO 12-hourly for 5–7 days.
- Use simple emollients. Aerosolized preparations are less painful to apply and limit topical spread of infection.
- Chlorhexidine and potassium permanganate soaks once or twice daily reduce excessive exudation.
- Secondary bacterial infection is common, so perform bacterial swabs daily to guide treatment. If clinical concern, have a low threshold to starting systemic antibiotic therapy.
- If concern of ocular involvement, liaise with the ophthalmologist early.
- Give oral nsAH for pruritus.
- If oral involvement, regular antiseptic and anti-inflammatory mouthwashes, with good analgesia.
- Avoid topical steroids for active dermatitis for at least 3–5 days until the infection is clinically resolving.

Practice points

Patients with severe atopic eczema should be advised about prompt treatment of herpes labialis and to avoid contact with individuals with active herpes simplex.

Patients with active herpes labialis should be advised to avoid contact with individuals with atopic eczema.

Psychiatric emergencies

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Acute confusion: assessment

Acute confusional states, or delirium, are relatively common. They are particularly common in care of the elderly and on orthopaedic wards. Risk factors include: age >65 years, prior cognitive impairment or dementia, multiple comorbidities, psychoactive drug use, polypharmacy, previous history of delirium/falls/CVA, and gait disorder. Acute confusion may occur on a background of chronic cognitive impairment (dementia) and may last for a prolonged period of days or even weeks. Acute confusion may occur as part of a mental illness or be secondary to organic disease (e.g. brain tumour or encephalitis).

Common features of acute confusion

- Rapid onset.
- Fluctuation.
- Clouding of consciousness.
- Impaired recent and immediate memory.
- Disorientation.
- Perceptual disturbance, especially in visual or tactile modalities.
- Psychomotor disturbance (agitation or ↓ movements).
- Altered sleep–wake cycle.
- Evidence of underlying cause.

Common causes of acute confusion

- Pain or discomfort (e.g. urinary retention, constipation).
- Hypoxia.
- Metabolic disorders (renal failure, liver failure, acidosis, hypercalcaemia, hypoglycaemia) or endocrine disease (thyrotoxicosis, Addison's disease, DM).
- Infection (systemic or localized).
- Cardiac (MI, CCF, endocarditis).
- Neurological (head injury, subdural haematoma, CNS infection, post-ictal states).
- Drugs [prescribed: benzodiazepines, opiates, digoxin, cimetidine, steroids, anti-parkinsonian drugs, anticholinergics; or recreational: especially stimulants, alcohol, gamma-butyrolactone (GBL), ketamine].
- Alcohol or drug withdrawal.

Detection of acute confusion

- The presence or absence of cognitive impairment may help distinguish between organic and functional mental impairment.
- The 10-point Abbreviated Mental Test Score, 30-point Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), or the Confusion Assessment Method (short version) give a rapid estimate of key cognitive functions.
- Take a clear history from friends or relatives, and try to determine whether delirium is superimposed upon dementia.

Practice points

Patients with visual hallucinations usually have organic confusion.

Acute confusion: management

- Treat the cause. Always consider alcohol withdrawal. Ensure that common problems like dehydration, pain, and constipation are adequately treated.
- It is often sufficient to manage the delirious patient's behaviour conservatively (non-pharmacologically), while treating the underlying cause. Nurse in a well-lit, quiet room with familiar nursing staff or, better still, a familiar person such as a family member or carer. Ensure effective communication and reorientation, and provide reassurance to patients with delirium.
- Occasionally, patients may refuse investigations or treatment. It may be important to go ahead with baseline investigations in order to rule out life-threatening causes for the confusion, and this may need to be done under the Mental Capacity Act 2005 or common law (➡ The Mental Health Act, p. 726; ➡ Common law, pp. 730–1).
- If sedation is required, use small amounts of sedatives, given orally if possible. Offer liquid preparations if tablets are refused. Parenteral medication may be indicated if patients refuse or are particularly disturbed. See ➡ Sedation for patients with delirium, pp. 714–15 for drugs and doses.
- Patients with ongoing disturbance may require regular sedation.

Sedation for patients with delirium

(See Box 13.1.)

- There are a few medication options here, so consider: the likely cause of delirium, concomitant medication, and any underlying comorbidities when choosing.
- Start with low doses, and titrate upwards according to clinical response.
- Antipsychotics are used, but not licensed for delirium, so this is off-label prescribing. However, some such as haloperidol have a licence for agitation in the elderly, and risperidone for short-term management of aggression in dementia. Haloperidol 0.5–1mg PO bd, with additional doses 4-hourly if needed. If using IM haloperidol 0.5–1mg, monitor for 1h and repeat if necessary. Remember it is recommended to have a pre-haloperidol ECG recorded due to risk of QT prolongation. Avoid haloperidol in neuroleptic malignant syndrome (NMS), anticholinergic toxicity, and hepatic failure. Olanzapine 2.5–5mg PO bd (max 20mg/24h) and risperidone 0.5mg bd (max 4mg/24h) can be used, but in the elderly with underlying dementia, there is an ↑ risk of CVA.
- Lorazepam 0.25–1mg PO/IM every 2–4h, as needed (half doses in the elderly), but remember that benzodiazepines may exacerbate confusion.
- Diazepam 5–10mg PO (2mg starting dose in the elderly).
- In patients with Lewy body dementia or Parkinson's disease, there is a high risk of severe extrapyramidal side effects, so best to avoid antipsychotics in these cases, and consider benzodiazepines.
- Some patients who are neuroleptic-naïve are extremely sensitive to neuroleptics and may develop severe extrapyramidal side effects. Use low doses of antipsychotics if you are unsure. Dystonic reactions should be treated with anticholinergic drugs such as procyclidine.
- If parenteral medications are required, use lorazepam and/or haloperidol (doses as listed earlier).

- Reassess the degree of sedation after 15–20min.
- Patients with heavy sedation require vital signs monitoring every 5–10min for the first hour, then half-hourly until they are ambulatory.

Prognosis in acute confusion

Delirium and dementia both carry adverse prognosis. In particular, delirium increases the length of hospital stay and is associated with significant mortality and may lead to residual cognitive impairment. It is important to ensure that cognitive assessment is repeated after the episode prior to discharge, as residual deficits may go undetected otherwise.

Box 13.1 Key points: sedation for patients with delirium and disturbed behaviour

Start with low doses, and titrate to clinical response.

- Oral medication options:
 - Haloperidol 0.5–1mg bd, with additional PRN doses every 4h if needed.
 - Atypical antipsychotics: risperidone 0.5mg bd, with additional PRN doses if needed every 4h (max 4mg/24h), or olanzapine 2.5–5mg od (max 20mg/24h).
 - Lorazepam 0.25–1mg every 2–4h (usual max 3mg/24h).
 - Diazepam: starting dose 5–10mg, start at 2mg in the elderly.
- Parenteral medication options:
 - Haloperidol 0.5–1mg IM, monitor for 1h, and repeat if necessary (peak effect 20–40min).
 - Lorazepam 0.25–1mg 2- to 4-hourly as needed (usual max 3mg/24h).
- Reassess the patient after 15–20min to assess the effects of sedation.
- Monitor vital signs every 5–10min for the first hour, then half-hourly until the patient is ambulatory.
- Patients with dementia with Lewy bodies or Parkinson's disease or those who are neuroleptic-naïve may develop severe extrapyramidal side effects with antipsychotics. Use alternatives or low doses initially, and treat any dystonic reactions with an anticholinergic drug (e.g. procyclidine).
- If this approach does not achieve sufficient management of an acutely disturbed behaviour or if the risks to self and others are imminent, consider rapid tranquillization (➡ Rapid tranquillization for acutely disturbed or violent patients, p. 716).

Rapid tranquillization for acutely disturbed or violent patients

Unfortunately, violent or dangerous situations do occur in medical settings. If a patient needs rapid sedation in order to keep them or others safe, consider this pathway.¹

A stepped approach: always try to use the least invasive option; however, go 'up' the steps, as required by the situation.

- 1 Attempt verbal and situational de-escalation.
- 2 Offer oral treatment: consider what medication the patient is already on. If on a regular antipsychotic, offer lorazepam 1–2mg, or buccal midazolam 10–20mg. Can be repeated after 45–60min. If not already on regular antipsychotics, then consider olanzapine 10mg, risperidone 1–2mg, or haloperidol 5mg. Note that for haloperidol use, it is now recommended to have a pre-haloperidol ECG due to risks of QT prolongation. Avoid combining two or more different antipsychotics.
- 3 If oral medication is refused or ineffective and the patient is placing themselves or others at significant risk, consider IM treatment—lorazepam 1–2mg, promethazine 50mg, olanzapine 10mg, aripiprazole 9.75mg, or haloperidol 5mg are all options. Whichever option is chosen, it can be repeated after 30–60min if insufficient effect.

Remember to have flumazenil to hand if using benzodiazepines in case of respiratory depression. IM olanzapine should not be combined with IM benzodiazepine. IM promethazine is useful in patients with benzodiazepine tolerance. Haloperidol should be the last choice due to higher rates of dystonic reactions and risks of QT prolongation (pre-treatment ECG formally recommended).

- 4 Consider IV treatment. Diazepam 10mg over at least 5min. Repeat after 5–10min if insufficient effect, up to three times. Remember to have flumazenil to hand.
- 5 If all the above have failed, seek expert advice from the consultant on-call or senior clinical pharmacist on-call.

Monitor for potential problems: acute dystonic reactions, respiratory depression, arrhythmias, bradycardia, hypotension, and ↑ temperature (withhold further antipsychotics, risk of NMS, check plasma creatinine kinase).

Monitoring after rapid tranquillization: monitor temperature, pulse rate, BP, and RR every 5–10min for the first hour, then every 30min until the patient is ambulatory. If the patient is unconscious, consider continuous pulse oximetry; ensure the airway is maintained; a nurse should be present until the patient is ambulatory.

Haematological monitoring and ECG monitoring are recommended if parenteral antipsychotics are given, especially if high doses are administered. Hypokalaemia, stress, and agitation can increase the risk of cardiac arrhythmia. All patients given haloperidol should have ECG monitoring.

Reference

1. Taylor D et al., (2015). *The Maudsley Prescribing Guidelines in Psychiatry*, 12th edn. South London and Maudsley NHS Foundation Trust and Oxleas NHS Foundation Trust, Wiley-Blackwell.

Acute alcohol withdrawal

(Also see 🔄 Acute alcohol withdrawal, pp. 436–7.)

It is estimated that there are between 1 and 2 million people in England who are alcohol-dependent. There is a spectrum of dependence, from mild to severe, and withdrawal symptoms occur also on a spectrum, often commensurate with the severity of dependence. Untreated, this carries a risk of seizures, permanent neurological complications, and death. Severe cases of dependence, cases complicated by other risks such as physical comorbidities and mental health problems, or when signs of delirium tremens (DT) or Wernicke–Korsakoff syndrome are present should be treated as a medical emergency.

Detection of alcohol withdrawal

Early clinical features include anxiety, restlessness, tremor, insomnia, sweating, tachycardia, ataxia, and pyrexia. Consider using the Clinical Institute Withdrawal Assessment of Alcohol (CIWA-Ar) scale to measure the degree of withdrawal. Withdrawal may be complicated by seizures, especially in those with known epilepsy and those with a prior history of withdrawal seizures. DT can develop and is characterized by confusion and disorientation, labile mood and irritability, hallucinations (auditory and visual), and fleeting delusions, often very frightening. Untreated, this condition carries a significant risk of death.

Do not forget to screen for Wernicke–Korsakoff syndrome, a complication of acute thiamine deficiency which occurs in chronic alcoholism. WE presents with acute confusion, ataxia, nystagmus, and ophthalmoplegia ± peripheral neuropathy. Not all of these symptoms need be present. Untreated, a large number of these patients will develop long-term memory problems from Korsakoff syndrome.

Treatment of alcohol withdrawal

- Uncomplicated and mild-to-moderate alcohol withdrawal patients can often be treated as outpatients by community drug and alcohol services.
- Consider inpatient or residential assisted withdrawal if a patient meets one or more of the following criteria. They:
 - Drink over 30U of alcohol per day.
 - Have a score of >30 on the Severity of Alcohol Dependence Questionnaire (SADQ).
 - Have a history of epilepsy or of withdrawal-related seizures or DT during previous assisted withdrawal programmes.
 - Need concurrent withdrawal from alcohol and benzodiazepines.
 - Regularly drink between 15 and 20U of alcohol per day and have:
 - significant psychiatric or physical comorbidities (e.g. chronic severe depression, psychosis, malnutrition, CCF, UA, chronic liver disease), or
 - a significant learning disability or cognitive impairment.
- Consider a lower threshold for inpatient or residential assisted withdrawal in vulnerable groups, e.g. homeless and older people.
- Any patient in withdrawal with signs of DT or Wernicke–Korsakoff syndrome needs to be admitted for urgent treatment.

- Alcohol withdrawal should be treated with chlordiazepoxide or diazepam (consider lorazepam or oxazepam if elderly or significant liver disease) or carbamazepine. If an IV agent is needed, use diazepam. B-complex vitamins are required to prevent WE. Prophylaxis for Wernicke's consists of parenteral therapy as Pabrinex® (one pair of ampoules od for 3–5 days IM or IV), and thereafter oral vitamin supplements should be given. In cases where evidence of Wernicke's is already present, give Pabrinex® two pairs of ampoules thrice daily IV for a minimum of 2 days, followed by 5 days of one pair of ampoules daily; continue as long as symptoms improve.
- Other useful drugs may include:
 - Atenolol or propranolol for hypertension.
 - Lorazepam for seizures.
 - Antipsychotics for hallucinations: not usually required. Use small doses and limit the duration. Haloperidol which has been previously used must be used with caution, as it may increase the risk of seizures, as well as having cardiovascular risks. Olanzapine may be an alternative.

Withdrawal regime

See 🔄 Acute alcohol withdrawal, pp. 436–7.

Aftercare

- Maintenance thiamine or multivitamin therapy should be given initially.
- Screen for residual cognitive impairment.
- Mobility and occupational therapy assessments before discharge may help if there are problems with the home environment.
- Identify the patient's local drug and alcohol service, and encourage the patient to self-refer.
- Some hospitals have alcohol liaison nurses who may be able to assist with counselling or follow-up. Non-National Health Service (NHS) organizations include the Alcoholics Anonymous (AA).

Practice points

Sudden onset of confusion and delirium with sweating and shaking, particularly in patients recently hospitalized, may indicate alcohol withdrawal. Check the serum PO_4^{3-} level, as it may be very low ($<0.4\text{mmol/L}$) in acute alcohol withdrawal and lead to confusion or profound weakness. It should be treated with IV phosphates to maintain a plasma concentration of $>0.4\text{mmol/L}$.

Neuroleptic malignant syndrome

- **Essence:** a rare, life-threatening, idiosyncratic reaction to antipsychotic (and other) medication (see Box 13.2), characterized by fever, muscular rigidity, altered mental status, and autonomic dysfunction. NB If diagnosed in a psychiatric setting, transfer the patient to acute medical services where intensive monitoring and treatment are available.
- **Pathophysiology:** theories: secondary to dopamine (DA) activity in the CNS, i.e. striatum (rigidity), hypothalamus (thermoregulation—by blockade of D₂-receptors or ↓ DA availability); impaired Ca²⁺ mobilization in muscle cells leads to rigidity (like malignant hyperthermia); sympathetic nervous system activation or dysfunction.
- **Epidemiology:** incidence 0.07–0.2% (pooled data); ♀:♂ = 2:1.
- **Mortality:** 5–20%—death usually due to respiratory failure, cardiovascular collapse, myoglobinuric renal failure, arrhythmias, or DIC.
- **Morbidity:** rhabdomyolysis, aspiration pneumonia, renal failure, seizures, arrhythmias, DIC, respiratory failure, worsening of a primary psychiatric disorder (due to withdrawal of antipsychotics).
- **Symptoms/signs:** hyperthermia (>38°C), muscular rigidity, confusion/agitation/altered level of consciousness, tachycardia, tachypnoea, hyper-/hypotension, diaphoresis/sialorrhoea, tremor, incontinence/retention/obstruction, creatinine kinase (CK)/urinary myoglobin, leucocytosis, metabolic acidosis.
- **Risk factors:** ↑ ambient temperature; dehydration; patient agitation or catatonia; rapid antipsychotic initiation/dose escalation; withdrawal of anti-parkinsonian medication; use of high-potency agents/depot IM preparations; history of organic brain disease (e.g. dementia, alcoholism), affective disorder, previous NMS; predisposing drugs (e.g. lithium, anticholinergic agents).
- **Differential diagnosis:** catatonia; malignant hyperthermia; encephalitis/meningitis; heat exhaustion; parkinsonism/acute dystonia; serotonergic syndrome; toxicity due to other drugs (e.g. amphetamine, MDMA, cocaine, antidepressants, antihistamines, sympathomimetics, salicylates); DT; rhabdomyolysis; septic shock; haemorrhagic stroke; tetanus; pheochromocytoma; strychnine poisoning.
- **Investigations:** FBC, blood cultures, LFTs, U&Es, Ca²⁺ and PO₄³⁻ levels, serum CK, urine myoglobin, AST and ALT (be aware that ALT increases in muscle injury), ABGs, coagulation studies, serum/urine toxicology, CXR (if aspiration suspected), ECG; consider head CT (intracranial cause) and LP (to exclude meningitis).
- **Management:** benzodiazepines for acute behavioural disturbance (NB use of restraint and IM injection may complicate the interpretation of serum CK). Stop any agents thought to be causative (especially antipsychotics), or restart anti-parkinsonian agents. Supportive measures: O₂, correct volume depletion/hypotension with IV fluids, reduce the temperature (e.g. cooling blankets, antipyretics, cooled IV fluids, ice packs, evaporative cooling, ice-water enema). Rhabdomyolysis—vigorous hydration and alkalinization of the urine

using IV sodium bicarbonate to prevent renal failure. Pharmacotherapy to reduce rigidity: dantrolene (IV 0.8–2.5mg/kg qds; PO 50–100mg bd), lorazepam (up to 5mg); second line: bromocriptine (PO 2.5–10mg tds, increase to max 60mg/day), amantadine (PO 100–200mg bd); third line: nifedipine; consider ECT (NB ↑ risk of fatal arrhythmias).

- *Course:* may last 7–10 days after stopping oral antipsychotics and up to 21 days after depot antipsychotics (e.g. fluphenazine).
- *Prognosis:* in the absence of rhabdomyolysis, renal failure, or aspiration pneumonia, and with good supportive care, prognosis is good.
- *Follow-up:* monitor closely for residual symptoms. Once symptoms have settled, allow 2+ weeks (if possible) before restarting medication (use low-dose, low-potency, or atypical agents). Consider prophylaxis (bromocriptine). Inform the patient about the risk of recurrence if given antipsychotic medication. Ensure this is recorded prominently in their medical notes.*

Box 13.2 Drugs reported to cause symptoms characteristic of NMS

- *Antipsychotics:* aripiprazole, chlorpromazine, clozapine (rarely), flupentixol, fluphenazine, haloperidol, olanzapine, promazine, quetiapine (rarely), risperidone, thioridazine.
- *Anti-parkinsonian agents:* amantadine (+ withdrawal), anticholinergics (withdrawal), levodopa (+ withdrawal).
- *Antidepressants:* amoxapine, clomipramine, desipramine, phenelzine, trimipramine, venlafaxine.
- *Other:* carbamazepine (+ withdrawal), ganciclovir, ferrous sulfate, lithium, methylphenidate, metoclopramide, oral contraceptives.

* Reproduced from Semple D, et al. *Oxford Handbook of Psychiatry*, 2013, with permission from Oxford University Press.

Dealing with violent patients

Occasionally, you may encounter violent patients in medical settings, and assaults on doctors and nurses do happen from time to time. Violence may be a symptom of a disorder (e.g. psychosis, post-ictal, acute confusion), or patients may be violent because of frustration, criminality, etc. Diagnosis is key because management is very different.

Predisposing factors

- Delirium.
- Dementia.
- Epilepsy.
- Brain damage (especially temporal or frontal lobes).
- Alcohol intoxication or withdrawal.
- Drugs (cocaine, crack, amphetamine, opiate, or sedative withdrawal).
- Acute psychotic episode.
- Personality disorder.
- Previous violent behaviour in patients with such conditions may give an indication of the future risk.

Management

Risks posed by violent patients may be minimized by following some simple rules.

- Do not see patients who may be violent in an isolated room, and do not see them on your own—ask a nurse or other professional to join you.
- Keep yourself between the patient and the door.
- If you are uncomfortable or afraid, end the interview and leave.
- It is usually sufficient to calm the patient down verbally and avoid confrontation.
- On occasion, it is necessary to sedate violent patients. See ➡ Rapid tranquillization for acutely disturbed or violent patients, p. 716, ➡ The Mental Health Act, p. 726, and ➡ Common law, pp. 730–1 for what legal frameworks and circumstances under which this can be done.
- Restraint may be required, particularly if sedation is needed; security and nursing staff may do this ± the police if necessary.
- If violence is part of an underlying psychiatric disorder, liaise with the psychiatric team about current and ongoing management.

Deliberate self-harm

Deliberate self-harm (DSH) is a common presenting complaint to A&E and reason for admission. The severity and sequelae of DSH vary greatly, from superficial cuts to serious ODs requiring prolonged spells in hospital. Suicide is uncommon, but DSH increases the risk of subsequent suicide (1% of those who commit acts of DSH kill themselves in the next year—100 times the general population risk), and 40–60% of suicides have a history of DSH. Assessment of patients who have harmed themselves is important in order to:

- Detect those at risk of subsequent DSH or suicide (see Box 13.3).
- Identify patients with significant mental health problems requiring treatment.
- Plan aftercare in hospital or in the community.

Assessment by general medical staff

Assessment of DSH is normally done by a psychiatrist, specialist nurse, or social worker experienced in the field. However, it is important for all staff to be able to make a basic assessment of these patients, because patients may refuse to see a mental health worker or may attempt to leave the ward or department before a detailed assessment can be carried out.

What if a patient wants to leave before they are assessed by a mental health professional?

- You have a duty of care to the patient that includes protecting them as best you can from ongoing risk.
- Try to persuade the patient to stay for an assessment. If they agree, refer to the psychiatric team and ask the nursing staff to monitor the patient.
- If the patient refuses, then you will need to ask them to stay while you make your own assessment of risk.
- If they will not stay, and you are concerned, you may need to detain them under common law, pending a formal psychiatric assessment.
- If they agree to stay, make your assessment. Do not forget to enquire about past episodes of self-harm and ongoing psychiatric problems, and drug or alcohol problems, as well as the questions already detailed.
- If, after your assessment, you have concerns that require the patient to see a mental health professional, try to persuade them to stay. If they refuse, consider their capacity to decide to leave under the MCA framework and whether you can use this to keep them from leaving, or consider detaining them under common law, pending an urgent psychiatric assessment.
- If you are satisfied that the ongoing risk is not of a magnitude that requires them to be detained, then allow them to be discharged, but ensure that the GP is informed.
- For detaining patients who will not stay in hospital, see ➡ Patients who do not wish to stay in hospital, p. 733.
- For guidelines on treatment for patients who are refusing treatment, see ➡ Mental Capacity Act 2005 (England and Wales), p. 728 and ➡ Common law, pp. 730–1.

Points to remember about DSH

- Risk assessment in older adults or children and adolescents requires specialist input. Always obtain advice in these cases.
- Staff attitudes towards patients who self-harm, especially if they do so frequently, can be very negative. Patients usually notice this. Try and maintain an empathic attitude and to understand what may motivate the behaviour, however difficult this may be.
- Some patients present repeatedly with DSH. These patients may have personality disorders, with or without substance misuse, and may be very difficult to manage. Most A&E departments know their frequent attendees well and have strategies in place for particular individuals—always ask.

Box 13.3 Questions to assess suicide risk after an act of self-harm

- Current mood and mood at the time of the act?
- Any forward planning, final acts, or suicide notes?
- Any precautions against being discovered?
- What was going through their mind at the time of the act?
- Did they mean to die?
- What is their view on having survived?
- What are their thoughts about the future now?
- Have they any feelings now that they wish to harm themselves? Have they made plans?

Practice points

The phrase 'detain under common law' is contentious. While a doctor who acted to prevent a patient from immediate harm, e.g. by stopping an acutely suicidal patient from leaving A&E, is unlikely to be criticized and could claim a common law defence of 'necessity' and 'best interests' if he were to, there is, strictly speaking, no power to detain under the common law.

The Mental Health Act

There is frequent confusion about the ability of patients with mental health problems to consent to, or refuse, medical treatment and what to do if a patient is acting in a way that will lead to self-harm or harm to others.

The Mental Health Act 1983 (revised 2007)

Different rules apply in Scotland, although the principles are the same—seek local advice.

This Act allows for the compulsory detention and/or treatment of patients with a mental disorder (defined as: any disorder or disability of the mind) of a nature and/or degree that requires inpatient treatment against their wishes. Thus, patients who need to be in hospital because of a risk to their health and safety or that of others may be detained or brought into hospital if the appropriate people agree that this is necessary.

- Section 2 allows a period of assessment and/or treatment for up to 28 days and is usually applied to patients presenting for the first time or known patients with a new problem.
- Section 3 (which may also follow Section 2) allows detention for treatment for up to 6 months.
- Patients have the right to appeal against both Sections 2 and 3. Both Sections require opinions from two appropriately qualified doctors and an approved mental health professional (AMHP).
- Section 4 allows patients to be brought to hospital with only one medical and one AMHP's opinion, and is only used in emergencies.
- Sections 5(2) and 5(4) apply to hospital inpatients (➡ Detaining a patient in an emergency, p. 734).
- Section 136 allows the police to detain people (in public places) with a suspected mental disorder and associated risks and bring them to a 'designated place of safety' (often a dedicated suite within a psychiatric hospital, but in some localities, this may be A&E or a police station) to be assessed by a doctor and an AMHP who may make them informal or arrange for a Section 2 or 3.

People may be detained under a Section either in the community or in hospital.

Remember: the Mental Health Act only allows treatment for mental health disorders against the wishes of patients, and not physical health problems.

Patients detained under the Mental Health Act often have capacity to decide whether to accept or refuse medical treatment, but if this is in doubt, then the Mental Capacity Act should be used to assess their capacity. If, according to the tests set out in the Mental Capacity Act, they do not have capacity, then treatment for physical health problems may be given against their wishes in accordance with the stipulations of the Mental Capacity Act (➡ Treating patients without their consent, p. 727).

Treating patients without their consent

The issue of whether and how to treat patients without their consent arises surprisingly often. It is frequently presumed that this is due to mental illness, although often this is not so.

What to do in this situation

The key to whether or not a patient is able to refuse treatment is whether or not they have capacity to do so. Every qualified medical doctor should be able to assess capacity; however, psychiatrists are frequently asked to do so or provide a second opinion in complex cases. In an emergency, it may not be possible to obtain specialist psychiatric advice, so you may need to act based on your assessment.

For a patient to have capacity to make a specific decision, they must be able to understand the information relevant to the decision; understand the alternative courses of action—and be able to weigh up the pros and cons of each; retain memory of decisions and the reasons for them; and communicate their intent (➡ Mental Capacity Act 2005 (England and Wales), p. 728).

Remember

- You are only assessing capacity for a specific decision (e.g. does the patient have capacity to refuse NAC treatment for paracetamol OD?); there is no overall/global capacity which a patient has or lacks.
- Patients may have the capacity to make some decisions and not others.
- Capacity in the same patient may fluctuate over time.

Mental illness or cognitive impairment may impair capacity but need not do so—there are legal precedents where patients who are mentally unwell have been wrongfully treated against their will. Disagreeing with medical advice does not automatically constitute incapacity.

If a patient does not have capacity and requires emergency treatment, then this may be given against their will under the Mental Capacity Act 2005 or under common law, depending on which is more appropriate.

Mental Capacity Act 2005 (England and Wales)

When considering treatment without a patient's consent, you need to assess their capacity to refuse the proposed treatment under the Mental Capacity Act framework. This has more safeguards for patients and doctors from a legal standpoint than the common law approach.

Five principles

- 1 A person must be assumed to have capacity, unless it is established that he lacks capacity.
- 2 A person is not to be treated as unable to make a decision, unless all practicable steps to help him to do so have been taken without success.
- 3 A person is not to be treated as unable to make a decision merely because he makes an unwise decision.
- 4 An act done, or decision made, under this Act for, or on behalf of, a person who lacks capacity must be done, or made, in his best interests.
- 5 Before the act is done, or the decision is made, regard must be had to whether the purpose for which it is needed can be as effectively achieved in a way that is less restrictive of the person's rights and freedom of action.²

Assessment of incapacity

Sections 2 and 3 of the Act set out a two-stage test for assessing incapacity.

- 1 A person lacks capacity if he is unable to make a decision for himself in relation to any matter because of a permanent or temporary impairment in the functioning of the mind.
- 2 A person is unable to make a decision for himself if he is unable to: understand the information relevant to the decision; retain that information for a sufficient period to make a decision; use or weigh that information as part of the process of making the decision; and communicate his decision.

Judgements about incapacity are to be made on the balance of probabilities. Lack of capacity is not to be presumed based on a person's age or appearance, on any aspect of his behaviour, or on any condition or disorder from which he suffers. The Act specifies certain decisions that cannot be made by one person on behalf of another. These are: agreeing to marriage, civil partnership or divorce, consent to a sexual relationship, and casting a ballot in an election.³

NB Section 6 of Mental Capacity Act allows the restraint of a patient who lacks capacity to make a particular decision, provided restraint is necessary to prevent harm to self and that the restraint is proportionate to the likelihood of the patient suffering harm and to the seriousness of the potential harm and that it does not constitute a deprivation of liberty.

If you assess someone as lacking capacity with regard to refusing urgent treatment and act under the best interests principle of the Mental Capacity Act and treat someone without their consent, make sure you document your capacity assessment and the rationale for your actions in the notes.

References

2. *Mental Capacity Act 2005*.  <https://www.legislation.gov.uk/ukpga/2005/9/section/1>
3. Semple D, Smyth R (2013). *Oxford Handbook of Psychiatry*, 3rd edn. Oxford University Press, Oxford.

Common law

- This allows medical practitioners to act in the patient's best interests in emergency situations where they are unable to give consent (e.g. if they are unconscious, or conscious but lack capacity—although if time permits, in cases where patients lack capacity, then the Mental Capacity Act framework should be used over common law).
- If in an emergency, it is deemed necessary to detain a patient pending assessment, it may be done under common law.
- Treatment under common law is given in the best interests of the patient if it is carried out to save life or to ensure improvement or prevent deterioration of physical or mental health.

Always document in the notes that you are giving treatment in the patient's best interests under common law.

Common law principles for medical treatment decisions

- *Act in accordance with the patient's wishes*: a fundamental principle of the doctor–patient relationship. Doctors should, in general, respect the patient's autonomy in decision-making, only acting against the patient's wishes in very limited circumstances.
- *Presume capacity in adults*: a patient over the age of 16 is presumed to have capacity to make treatment decisions, unless there is evidence to the contrary (assessed on the balance of probabilities).
- *Apply the 'reasonableness' test*: a frequently used consideration in law is the test of what a hypothetical 'reasonable man' would do in the circumstances. For medical treatment decisions, the test is what the 'reasonable doctor' would have done in those circumstances.
- *Act in the patient's 'best interests'*: in emergency situations, it may not be possible to obtain consent (e.g. in an unconscious RTA victim requiring drainage of an extradural haematoma); here, it is accepted that the doctor's overriding duty is to preserve life.
- *Doctrine of necessity*: 'necessity' provides a defence against a potential criminal charge that you have assaulted a patient by giving non-consensual treatment. A doctor may therefore give emergency treatment to preserve life and prevent significant deterioration in health.
- *Act in accordance with a recognized body of opinion*: it is accepted in law that medicine is not an exact science—that, in any situation, multiple courses of action may be potentially reasonable. However, there is an expectation that any treatment decision is considered suitable by a body of professional opinion (the 'Bolam test').
- *Act in logically defensible manner*: the Bolitho case added a consideration to the Bolam test by stating that medical decisions made must, in addition to being in accordance with a recognized body of opinion, be logically defensible in the circumstances.

- *Consider use of applicable law:* the treating doctor should consider whether the provisions of any statute law provide guidance and additional protections for the patient. However, they should not delay urgent treatment to enact the provisions of statute law.
- *Consider a request for court judgement:* in difficult situations, consult more experienced colleagues; where appropriate, seek legal advice on whether it is appropriate to apply to the court for a ruling.⁴

References

4. Semple D, Smyth R (2013). *Oxford Handbook of Psychiatry*, 3rd edn. Oxford University Press, Oxford.

The law on consent and capacity

- There is no such thing as proxy consent for adults in the UK; a third party cannot make a decision on a patient's behalf, though it is good practice to take their views into consideration, both under common law and the Mental Capacity Act best interests principle.
- The Mental Health Act 1983 (revised 2007) does not allow doctors to treat mentally impaired patients against their will for physical problems. The Scottish Act allows a broader view of allowable treatments and may well include treatment of self-poisoning (implied in the code of practice) and certainly does include treatment of delirium and starvation syndrome in anorexia, for example.
- Different rules apply to children and individuals with advance directives—you must always obtain specialist advice in such cases.
- Treating a patient who has capacity to refuse against their will can constitute a criminal offence. However, you are unlikely to be criticized for taking a decision to give lifesaving treatment against a patient's will if you are unsure about capacity. Most people would acknowledge that it is better to treat than not to treat in such situations.
- In any situation where you are unsure what to do, obtain senior advice at an early stage. Some of the medical defence organizations offer legal advice on a 24h basis.

Patients who do not wish to stay in hospital

Sometimes patients do not wish to stay in hospital. Usually the problem can be discussed, and an agreement can be reached between the patient and the medical team. From time to time, this is impossible. If a patient is acutely confused, they may not be willing to stay and require physical restraint in order to keep them there. In the case of patients who have harmed themselves, teams may be concerned about the possible risks to the patient if they leave the ward.

What to do in this situation

- Assess the patient. What are the medical issues that require them to stay? Is their wish to leave a symptom or part of an organic illness that needs to be treated? What are the potential risks to self or others if the patient leaves?
- Is it possible to reason with the patient and persuade them to stay?
- If not, assess whether they have capacity to decide to leave. If you are unsure or it is a complex case or one involving a psychiatric patient, ask for a psychiatric second opinion.
- If the patient tries to leave before a psychiatric assessment, they may be detained under common law.
- If the wait for a psychiatric opinion is likely to take a long time (e.g. no psychiatric team on site), it may be necessary for them to be detained. Hospital inpatients may be detained by a nurse under Section 5(4) of the Mental Health Act or by a single doctor under Section 5(2). Patients in A&E departments must be detained under common law or the Mental Capacity Act if appropriate.
- If the patient leaves (e.g. they ran past security guards before they could stop them) and you have significant concerns over their safety or that of the public (i.e. you can breach confidentiality), inform your seniors and consider informing the police. If you contact the police, ensure you can provide as much detail as possible (name, age, physical appearance, clothing, last known movements, address, etc.), as well as specific concerns (e.g. he said he wanted to jump off London Bridge), to assist in finding the patient. Inform the psychiatric team involved if the concerns are over mental health or if the patient is already under psychiatric community care so that they may follow up on the attendance to A&E/premature self-discharge.
- If the patient has capacity to refuse ongoing treatment and is not detainable under the Mental Health Act, then they may be allowed to leave against medical advice. It is often possible to get them to sign a form to that effect; if not, it should be documented that their self-discharge was against medical advice.

Detaining a patient in an emergency

Common law

If you believe it is in the interests of the patient not to be allowed to leave, and you are unsure about their capacity and therefore not able to use the Mental Capacity Act framework, the security staff may be asked to prevent them from doing so. Document that you are doing this under common law. This should take place until a psychiatric opinion may be obtained.

Section 5(2)

- This section allows an inpatient on any ward to be prevented from leaving. It lasts a maximum of 72h and is only a holding measure, pending a full Mental Health Act assessment by appropriate doctor(s) (usually two doctors) and an AMHP.
- Any registered medical practitioner may use Section 5(2), not only a psychiatrist. It must be applied by the consultant under whose care the patient currently is or their 'nominated deputy', i.e. a member of their team or whoever is covering their patients out of hours. It is actioned by filling in Form H1 (these should be available on the ward) which should be delivered to the local Mental Health Act administration office as soon as it is practicable.
- If a patient has been placed under Section 5(2), the duty psychiatric team should be informed, as should the AMHP, to ensure that the patient is reassessed appropriately and quickly. Section 5(2) expires once the patient has been seen by an appropriately qualified doctor approved under Section 12 of the Mental Health Act and rescinded, or converted to Section 2 or 3 following a Mental Health Act assessment.
- Section 5(2) does not allow you to enforce medical treatment of any kind. This would need to be given under common law or the Mental Capacity Act if the patient is not consenting.

Section 5(4)

- This Section entitles a suitably qualified nurse to hold a patient for up to 6h, pending the arrival of a doctor to assess the patient for Section 5(2). It is only used in situations where a doctor cannot arrive quickly, e.g. if they are off site.
- If the doctor decides that the patient needs to be held under Section 5(2), then the 72h duration of this latter Section begins at the time the nurse imposed Section 5(4). It ends once the patient has been assessed by appropriate mental health professionals regarding further detention or being made informal.
- Sections 5(2) and 5(4) are only applicable to inpatients, not to patients in A&E or outpatients. Patients in these areas are detained under common law, pending psychiatric assessment.

Practice points

It is best to detain people under common law if you do not think that they should leave the A&E department (see ➡ Common law, p. 730–1 for details of the principles used). You are unlikely to be criticized for this, and you may ensure their safety in the short term.

Mentally ill patients in hospital

Patients with chronic mental illnesses, such as schizophrenia, are at ↑ risk of ill health, compared with the general population, and frequently require care from general physicians.

Guidelines for looking after patients with mental illness

- Hospital is frightening for all patients. Mentally ill patients may require a lot of reassurance and explanation about what is happening to them.
- If people are on regular psychotropic medications, then *give them*. They will usually be able to tell you what they take and when. Remember that sudden discontinuation of certain medications, such as lithium, clozapine, and SSRIs, can precipitate mental health crises.
- Some patients are on depot injections, rather than tablets. Find when their next injection is due and, if this falls during their hospital stay, ensure that they receive it.
- If there is a reason for stopping a drug used in psychiatry, you should ask advice. Ideally, this should be from the psychiatrist and prescriber.
- It is good practice to communicate with the mental health team who know the patient, who will probably be based in the community. They will have a consultant and may have a social worker, community psychiatric nurse, or other keyworker who will appreciate knowing that their patient is in hospital.
- Communicate discharge plans to the community team—it may help you to speed up the discharge, as community support may already be in place.

Remember, if you are ever unsure about a patient's mental state, it is best to talk to a psychiatrist about it and ask for the patient to be reviewed, if necessary.

Sectioned patients on medical wards

Occasionally, patients who are in hospital under a Section of the Mental Health Act 1983 (revised 2007) become medically unwell. They may need to be transferred to, and cared for on, a medical, rather than a psychiatric, ward at these times. Please remember the following.

- Patients who are detained are likely to be seriously mentally unwell and therefore prone to becoming disturbed.
- It is acceptable for patients to be detained on a medical, rather than a psychiatric, ward under their Section if that is where they need to be, but you should expect ongoing input from the psychiatric team caring for the patient during their stay.
- Patients who are under a Section should be nursed by a mental health nurse at all times, alongside the general ward nurses. If a patient presents particular risks or is very disturbed, >1 nurse may be required.
- Ensure that the psychiatric team looking after the patient are kept informed of the patient's progress, so that their transfer back to the psychiatric unit and their ongoing medical care may be coordinated smoothly.
- Many psychiatric wards have neither the staff nor the equipment to perform even basic procedures (e.g. IV drips, monitoring). Patients going back to these wards need to be well stabilized medically before they return.

Practice points

- Always find out what medication a psychiatrically disturbed patient is taking. It is dangerous to stop certain psychotropic medications.
- New onset of confusion is organic until proven otherwise. Have a low threshold for starting aciclovir or other antiviral therapy until herpes encephalitis is excluded.

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Overdoses: general approach

- ODs account for 10–15% of acute medical emergencies and result in 140 000 admissions to hospital each year in England and Wales.
- In the last 15 years, the incidence of poisoning has ↑.
- Thirty per cent of self-poisonings involve multiple drugs.
- Fifty per cent of patients will have taken alcohol as well.
- It has been well documented that the history taken following an OD is often inaccurate with regard to the dose and timing of ingestion.
- Question any witnesses or family about where the patient was found and any possible access to drugs.
- Examination may reveal clues as to the likely poison (e.g. pinpoint pupils with opioids). Signs of solvent or ethanol misuse and IV drug use should be noted.

Management

- Priorities are to:
 - 1 Resuscitate the patient.
 - 2 Reduce absorption of the drug, if possible.
 - 3 Give a specific antidote, if available.
- Secure the airway (place in the recovery position), and monitor breathing, BP, temperature, acid–base, and electrolytes, and treat seizures or dysrhythmias; check BM in all drowsy patients. Intubate if not protecting the airway and not reversible with naloxone. Flumazenil should not be used diagnostically in the unconscious patient (see Table 14.1).

Table 14.1 Signs of poisoning in the unconscious patient

Sign	Consider
<i>Hypoventilation</i>	Opioids, ethanol, benzodiazepines, GHB/GBL
<i>Pinpoint pupils</i>	Opioids, organophosphates
<i>Dilated pupils</i>	Anticholinergics, tricyclic antidepressants, stimulants (e.g. amphetamine, cocaine)
<i>Bradycardia</i>	β-blockers, digoxin, GHB/GBL, calcium channel blockers, organophosphates
<i>Tachyarrhythmias</i>	Tricyclic antidepressants, anticholinergics, caffeine, theophylline, digoxin, stimulants (e.g. amphetamine, cocaine), local anaesthetics, antipsychotics
<i>Hyperthermia</i>	MDMA, amphetamines, anticholinergics, SSRIs
<i>Pyramidal signs, ataxia, hypertonia, hyper-reflexia, and extensor plantars</i>	Tricyclics or anticholinergic agents
<i>Hypertension</i>	Cocaine, amphetamines, ecstasy

NB Occasionally, patients present where poisoning is suspected but not known. Even where the history suggests self-poisoning, be aware that a serious underlying disease may be present. For example, patients who feel very ill will often self-medicate with aspirin and paracetamol.

- Take account of any active medical problems that the patient may have, e.g. IVDUs may have concurrent septicaemia, hepatitis, endocarditis, pulmonary hypertension, or HIV-related disease.
- Measures to reduce gut absorption include:
 - *Gastric lavage*: has an extremely limited role and may be associated with significant complications. It should only be used within 1h of a potentially life-threatening OD by clinicians with sufficient clinical experience. It is contraindicated in corrosive or hydrocarbon ingestion to enable its use.
 - *Activated charcoal* (50g as a single dose): will adsorb most drugs if given within 1h of ingestion, although its effectiveness falls off rapidly thereafter. Drugs *not* adsorbed by charcoal include iron, lithium, alkalis, acids, alcohols (e.g. ethanol, methanol, ethylene glycol), and organic solvents.
 - *Multiple-dose activated charcoal* (50g every 4h or 25g every 2h): increases whole body clearance of some drugs by interrupting enterohepatic or enteroenteric cycling, e.g. phenobarbital, carbamazepine, dapsone, quinine, and theophylline. Multiple-dose charcoal may also be used in slow-release drug OD (e.g. theophylline, calcium channel blockers).
 - *Whole bowel irrigation*: Klean-Prep®, a solution of polyethylene glycol (not to be confused with ethylene glycol!!) is given PO or by NG tube at 2L/h in adults. It is continued until the rectal effluent becomes clear.
 - *Indications*: ingestion of sustained-release or enteric-coated preparations of toxic drugs such as calcium channel blockers, lithium, iron. Percutaneous endoscopic gastrostomy (PEG) bowel lavage may be used in body packers to hasten the passage of packets of illicit drugs.
 - *Contraindications*: bowel obstruction, perforation, ileus, or in seriously ill patients, e.g. haemodynamic instability.
 - *Ipecac-induced emesis*: is no longer used.

Advice about management of the poisoned patient is available on TOXBASE® (☞ <http://www.toxbase.org>), the online database of the National Poisons Information Service (NPIS). For uncommon ODs or unstable patients, always seek telephone advice from the NPIS (telephone number inside the front cover of the *BNF* and on TOXBASE®).

Drug overdoses and antidotes

(See Table 14.2.)

Table 14.2 Antidotes that should be available in all emergency departments in all hospitals.*	
Antidote/drug	Indication
Acetylcysteine	Paracetamol
Activated charcoal	Many oral poisons
Atropine	Organophosphorus or carbamate insecticides; nerve agents Bradycardia
Calcium chloride	Calcium channel blockers Systemic effects of hydrofluoric acid
Calcium gluconate gel	Local infiltration for hydrofluoric acid
Dicobalt edetate	Cyanide antidotes
Hydroxocobalamin (Cyanokit®)	O ₂ should be administered in all cases Dicobalt edetate is the antidote of choice in severe cases when there is a high clinical suspicion of cyanide poisoning, e.g. after cyanide salt exposure Hydroxocobalamin (Cyanokit®) should be considered in smoke inhalation victims who have severe lactic acidosis, are comatose, are in cardiac arrest, or have significant cardiovascular compromise
Sodium nitrite	Sodium nitrite may be used if dicobalt edetate is not available
Sodium thiosulfate	Sodium thiosulfate is used generally as an adjuvant to other antidotes.
Flumazenil	Reversal of iatrogenic over-sedation with benzodiazepines Should not be used as a 'diagnostic' agent and is contraindicated in mixed tricyclic antidepressant/ benzodiazepine ODs and in those with a history of epilepsy
Glucagon	β-adrenoceptor-blocking drugs Other indications, e.g. calcium channel blocker/ tricyclic antidepressants
Intralipid® 20%	Severe systemic local anaesthetic toxicity
Methylthioninium chloride (methylene blue)	Methaemoglobinaemia
Naloxone	Opioids
Procyclidine injection	Dystonic reactions

Table 14.2 (Contd.)

Antidote/drug	Indication
Sodium bicarbonate 8.4% and 1.26% or 1.4%	Tricyclic antidepressants and class Ia and Ic antiarrhythmic drugs As part of urinary alkalization
Viper venom antiserum, European	European adder, <i>Vipera berus</i>
Calcium folinate	Methotrexate Methanol Formic acid
Cyproheptadine	Serotonin syndrome
Dantrolene	NMS, serotonin syndrome
Desferrioxamine	Iron
Digoxin-specific antibody (DigiFab®)	Digoxin and related glycosides
Fomepizole (or ethanol) (IV or PO)	Ethylene glycol and methanol Fomepizole is the antidote of choice in view of the difficulty in maintaining and monitoring ethanol infusions
Idarucizumab	Dabigatran-related active bleeding (discuss with local haematologists and the NPIS)
Macrogol '3350' (polyethylene glycol) Klean-Prep®	Whole bowel irrigation for agents not bound by activated charcoal, e.g. iron, lithium; also for body packers and for slow-release preparations
Mesna	Cyclophosphamide
Octreotide	Sulfonylureas
Phentolamine	Digital ischaemia related to injection of adrenaline Resistant hypertension caused by sympathomimetic drugs of abuse, MAOIs, and clonidine
Phytomenadione (vitamin K1)	Vitamin K-dependent anticoagulants
Protamine sulfate	Heparin
Pyridoxine	High-dose isoniazid

* Source: data from The College of Emergency Medicine & NPIS Guideline 2017.

Anticonvulsant drugs

Phenytoin

Phenytoin is an anti-epileptic and a class Ib antiarrhythmic, and it inhibits voltage-dependent Na^+ channels. It is highly protein-bound, and its metabolism via the liver demonstrates saturable (Michaelis–Menten) kinetics.

Presentation

- Nausea and vomiting are common early features.
- Horizontal nystagmus (the *sine qua non* of phenytoin toxicity) is seen, as concentrations increase.
- Dysarthria, drowsiness, nystagmus, ataxia, tremor, hyper-/hyporeflexia, and in significant poisoning coma, opisthotonus, vertical nystagmus, and convulsions.

Cardiovascular effects are rare after oral phenytoin OD (they occur with rapid IV phenytoin injection and are due to the propylene glycol diluent).

Management

- **Activated charcoal** (50g for adults) if the patient presents within 1h of ingestion of a toxic amount. Evidence from volunteer studies suggests that multiple-dose activated charcoal might provide some benefit, but there are no controlled data in patients with phenytoin poisoning. Plasma phenytoin concentrations can be helpful in monitoring patients with significant poisoning managed with multiple-dose activated charcoal; symptomatic toxicity generally occurs with phenytoin concentrations $>20\text{mg/L}$ and severe toxicity with concentrations $>40\text{mg/L}$.
- Observe for a minimum of 4h.
- All patients should have a 12-lead ECG (measure QRS and QT), and symptomatic patients should have bloods for U&Es, LFTs, and glucose.
- Seizures should be treated with IV diazepam in the first instance.
- Phenytoin is highly protein-bound, and so dialysis and plasmapheresis have no place in management.

Carbamazepine

OD with carbamazepine causes primarily dose-dependent CNS toxicity. Absorption is unpredictable, and it may take 6–12h for peak levels to be reached; secondary peaks can occur in patients with significant toxicity.

Presentation

- Nystagmus, dilated pupils, hyper-reflexia, ataxia, seizures, intention tremor, and dysarthria are common. Coma may present 8–12h later and may be cyclical and associated with respiratory depression and seizures.
- ECG abnormalities, including prolonged PR, QRS, and/or QTc, can occur, and in patients with severe poisoning, arrhythmias and hypotension can occur. Hyponatraemia and hypokalaemia can be present in those with severe poisoning.

Management

- Multiple-dose activated charcoal is indicated if $>20\text{mg/kg}$ have been taken and/or in symptomatic patients.
- Observe for at least 6h after a non-sustained related ingestion and 12h after a sustained-release ingestion.
- Plasma carbamazepine concentrations can be useful in patients treated with multiple-dose activated charcoal (concentrations $>40\text{mg/L}$ can be associated with severe toxicity).
- All patients should have an ECG to look for AV block and QRS and/or QTc prolongation. Patients with ECG abnormalities should be discussed with a poisons centre or a clinical toxicologist.
- Charcoal haemoperfusion and/or haemodialysis may have a role in life-threatening toxicity; these patients should be discussed with a poisons centre or a clinical toxicologist.

Sodium valproate

ODs of $<5\text{g}$ are unlikely to cause toxicity. Fatalities have occurred after ingestion of 20g. Plasma concentrations peak around 4h after dosing, but the half-life will be prolonged in OD.

Presentation

- Drowsiness is common, and coma can occur in large ingestions.
- Nausea, vomiting, abdominal pain, diarrhoea, and hypotension.
- Unlike other anticonvulsants, nystagmus is uncommon.
- Electrolyte abnormalities include hypernatraemia, hypoglycaemia, hyperammonaemia, and hypocalcaemia.
- Delayed-onset cerebral oedema can occur at 12–72h post-ingestion in those with severe poisoning.
- Haemorrhagic pancreatitis can also occur.

Management

- Supportive care is likely to be all that is needed, unless the patient has severe valproate poisoning. Activated charcoal (50g) can be given if OD taken within an hour.
- Monitor U&Es, Ca^{2+} , and glucose levels, and in those with severe poisoning, check ammonia levels.
- Seizures should be treated with IV diazepam.
- Hypotension may need treatment with fluids $\pm$ inotropes/vasopressors.
- Consider giving levocarnitine in patients with hyperammonaemia or hepatotoxicity.
- Haemodialysis may be of value in massive ODs.

Practice points

Unlike phenytoin toxicity, dysarthria, nystagmus, and ataxia are not seen in sodium valproate toxicity.

Newer anticonvulsants

- Lamotrigine, levetiracetam, pregabalin, vigabatrin, topiramate, tiagabine, oxcarbazepine, gabapentin.

Clinical presentation

- Drowsiness is found almost universally with these agents but is rarely severe, although coma can occur with pregabalin.
- Gabapentin OD may cause nausea and vomiting.
- Ataxia may be seen in lamotrigine and topiramate OD.
- Seizures may occasionally be seen in toxicity with lamotrigine, tiagabine, and topiramate.

Management

- *Activated charcoal* should be considered if the OD is taken within 1h.
- *Monitor* U&Es and glucose.

Antipsychotic drugs

Chlorpromazine, haloperidol, risperidone, olanzapine

All of these drugs have antipsychotic activity with dopamine receptor antagonist activity. Their pattern of toxicity and management are similar.

Presentation

Includes drowsiness, coma, extrapyramidal features (oculogyric crises, torticollis, trismus, and orolingual dyskinesia), myoclonus, hypotension (or rarely hypertension), and seizures. Many antipsychotic drugs cause QT prolongation and torsades de pointes (particularly amisulpride and haloperidol).

Management

Includes essential OD management and symptom-directed and supportive treatment.

- Consider *activated charcoal* (50g for adults) if the patient presents within 1h of ingestion of a toxic amount.
- Treat hypotension with IV fluids and raising the foot of the bed. Some patients may need inotrope/vasopressor support.
- Seizures usually respond to diazepam (5–10mg IV initially); resistant seizures are likely to require barbiturates.
- Treat any ECG features, as required:
 - For severe QRS prolongation (>160ms), give IV sodium bicarbonate 8.4% (50mL).
 - For severe QT prolongation (>500ms), give IV magnesium sulfate (2g) over 15min.
 - For torsades de pointes, give IV magnesium sulfate (2g) or use overdrive pacing.
- Treat extrapyramidal symptoms, e.g. acute dystonic reactions with anticholinergic agents, e.g. procyclidine (5–10mg IV).

Aspirin

Aspirin is now less commonly ingested in OD. Occasionally, poisoning follows the topical application of salicylic acid in keratolytics or the ingestion of methyl salicylate ('oil of wintergreen'). Its primary toxic effect is to uncouple oxidative phosphorylation.

Presentation

- The typical features of moderate salicylate toxicity are sweating, vomiting, epigastric pain, tinnitus, and blurring of vision.
- In adults, there is also an early increase in RR, causing alkalosis that precedes the later development of metabolic acidosis; children are more likely to develop an early pure metabolic acidosis.
- In severe OD, acidosis reduces the ionization of salicylic acid, which enhances tissue penetration. In the CNS, this presents as agitation, tremor and fits, coma, and respiratory depression. This also decreases renal salicylate clearance.

Complications

- Metabolic acidosis.
- Pulmonary oedema (non-cardiogenic, ARDS).
- ARF.
- Abnormal clotting due to hypoprothrombinaemia is very rare.
- Significant GI bleeding is surprisingly infrequent.

Prognostic features

- It is important that plasma salicylate concentrations are interpreted in the context of clinical features and the patient's acid–base status.
- Significant toxicity is unlikely at peak salicylate concentrations $<350\text{mg/L}$.
- Salicylate concentrations of $500\text{--}750\text{mg/L}$ represent moderate toxicity, and $>750\text{mg/L}$ (5.4mmol/L) severe toxicity; but severe features can be seen at lower salicylate concentrations in patients with metabolic acidosis and in children (<10 years)/the elderly (>70 years).
- Severe metabolic acidosis is associated with a poor outcome.

Management

- Take blood for U&Es, PT, and salicylate (and paracetamol) concentration at 4h after ingestion (repeat every 3–4h in symptomatic patients and in those with a salicylate concentration of $>350\text{mg/L}$ later to assess continued absorption, as tablets may adhere to form large masses in the stomach or some preparations are enteric-coated).
- Activated charcoal should be given if $>125\text{mg/kg}$ of aspirin has been taken in the last hour.
- If after 4h, salicylate levels are continuing to rise, a further dose of *activated charcoal* may be given to patients to prevent late absorption.
- Check ABGs to assess the acid–base status.
- Mild or moderate salicylate OD requires only PO or IV rehydration, with particular attention to K^+ supplements.

- Patients with significant clinical features and a salicylate concentration of $>500\text{mg/L}$ should be treated with:
 - Urinary alkalization to get urine pH to 7.5–8.5. Regimens include 225mmol of sodium bicarbonate (225mL of 8.4% over 60min or 1.5L of 1.26% over 2h), repeated as necessary to keep the urine at pH 7.5–8.5; further boluses of bicarbonate may be required in patients with a significant base deficit. This may cause hypokalaemia, which will limit urinary alkalization. Check serum K^+ levels every 2–3h.
 - Forced alkaline diuresis is no more effective and is potentially dangerous.
 - Haemodialysis is indicated for patients with severe poisoning—a salicylate concentration of $>900\text{mg/L}$ (6.51mmol/L) and particularly if associated with persistent or progressive acidosis, deteriorating level of consciousness, convulsions, non-cardiogenic pulmonary oedema, and renal or cardiac failure.
- Pulmonary oedema may indicate either fluid overload or $\uparrow$ vascular permeability; this is a bad prognostic feature in salicylate poisoning. Admit to ITU and monitor cardiac output. Non-cardiogenic pulmonary oedema may require CPAP or mechanical ventilation (➡ Mechanical ventilation, p. 828), and these patients are also likely to require haemodialysis.

Benzodiazepines

Deliberate OD with this group of compounds is very common. Unless combined with other sedatives (e.g. alcohol, opioids, tricyclic antidepressants), effects of a benzodiazepine OD are generally mild.

Presentation

- Drowsiness.
- Slurred speech.
- Hypotension (mild).
- Ataxia.
- Coma.
- Respiratory depression.

The elderly and those with chronic lung disease are generally more susceptible to cardiorespiratory depression with benzodiazepine OD.

Management

- If patients present within 1h, give 50g of *activated charcoal*. Ensure the patient can protect their airway.
- Flumazenil should not be used diagnostically in comatose patients where the diagnosis is uncertain or if mixed ODs are a possibility, as it may cause seizures, arrhythmias, or death—particularly if the patient has co-ingested a proconvulsant or proarrhythmic drug (e.g. dextropropoxyphene, theophylline, tricyclic antidepressants).
- If it is certain that a pure benzodiazepine OD has been taken, flumazenil may be used to reverse significant cardiorespiratory depression in severe OD, i.e. those with significant CNS depression associated with respiratory depression and hypoxia. It should generally only be given after consultation with a doctor experienced in its use or a poisons centre/clinical toxicologist. *Flumazenil* is given as an IV bolus of 0.2mg. If no response, give further IV bolus doses of 0.3mg and thereafter 0.5mg, to a maximum of 3mg, until the patient has an adequate RR. Most benzodiazepines have a substantially longer duration of action than flumazenil, and an IVI of 0.1–0.4mg/h will be needed to prevent early re-sedation.
- Avoid giving excess flumazenil to completely reverse the effect of benzodiazepines. In chronic benzodiazepine users, this can precipitate withdrawal.

Beta-blockers

These agents competitively antagonize the effects of endogenous catecholamines. They cause profound effects on AV conduction and myocardial contractility, and their effects are predictable based on their known pharmacology.

Presentation

- Sinus bradycardia.
- Hypotension.
- Cardiac failure.
- Cardiac arrest (asystole or VF).
- Hypoglycaemia (rare).
- Bronchospasm (rare in non-asthmatics).
- Lipid-soluble β -blockers (e.g. propranolol, carvedilol, labetalol, metoprolol, and pindolol) are more likely to cross the blood–brain barrier, causing CNS features, e.g. drowsiness, confusion, seizures, hallucinations, and coma.
- Sotalol causes QT prolongation and can cause torsades de pointes.

Prognostic features

- Subjects with pre-existing impaired myocardial contractility are less likely to tolerate an OD of β -blockers.

Management

- Establish IV access.
- Check a 12-lead ECG, and then monitor ECG continuously for at least 6h (12h for sustained-release OD).
- Record the HR and BP regularly (at least every 15min).
- Consider *activated charcoal* (50g for adults) if the patient presents within 1h of ingestion.
- *Hypotension*: seek expert help early, with early admission to critical care; raise the foot of the bed, and give an appropriate fluid challenge.
- If persistent hypotension, give IV glucagon (50–150 micrograms/kg, followed by an infusion of 1–5mg/h). This peptide exerts an inotropic effect, independent of β -receptor activation, by increasing myocardial cyclic adenosine monophosphate (cAMP) levels.
- Use of an intra-aortic balloon or an alternative cardiac support device may provide an adequate cardiac output, while the drug is metabolized and excreted.
- *Bradycardia*: may respond to atropine (0.5–1.2mg for an adult, repeated if required) or to glucagon in the doses discussed above. Pacing may be required in patients with persistent bradycardia associated with cardiovascular compromise (a high threshold is often required) (➡ Pulmonary artery catheterization 1, pp. 800–1; ➡ Pulmonary artery catheterization 2, p. 802; ➡ Pulmonary artery catheterization 3, p. 804).
- *Convulsions*: give diazepam 5–10mg IV initially (➡ Status epilepticus (tonic–clonic) 1, pp. 408–9).
- *Bronchospasm*: treat initially with nebulized salbutamol (2.5mg).
- *Monitor blood glucose* regularly (hourly BMs) in symptomatic patients. If hypoglycaemia develops, give PO or IV glucose.

Calcium channel blockers

Nifedipine, amlodipine, verapamil, and diltiazem

The most important effects are on the cardiovascular system. Only 3–4 times the recommended dose can cause severe toxicity. Calcium channel blockers block L-type Ca^{2+} channels that are present in cardiac and vascular tissues and the β -cells of the pancreas.

Presentation

- Non-cardiovascular effects are less common but may include nausea, vomiting, dizziness, agitation, and confusion. Metabolic acidosis, hyperkalaemia, hypocalcaemia, and hyperglycaemia can occur. The degree of hyperglycaemia correlates with the severity of poisoning.
- Severe hypotension secondary to peripheral vasodilatation and direct myocardial suppression is common. This may be associated with reflex tachycardia. Bradycardia and AV block may be present in severe poisoning.

Management

- Consider activated charcoal (50g for adults) if the patient presents within 1h of ingestion of a toxic amount.
- If sustained-release preparations have been used, consider whole bowel irrigation with polyethylene glycol or Klean-Prep®.
- Monitor BP and cardiac rhythm. Check U&Es, Ca^{2+} , glucose, and ABGs.
- Perform a 12-lead ECG and further ECGs if a slow-release preparation has been ingested or there is a fall in HR or BP.
- Asymptomatic patients should be observed for at least 12h after ingestion (24h for a sustained-release preparation).
- Give atropine for symptomatic bradycardia (1mg for adults). Repeat doses may be needed.
- Hypotension: seek expert help early, with early admission to critical care; raise the foot of the bed, and give an appropriate fluid challenge.
- Give calcium chloride (10mL 10%), and repeat 3–4 times if hypotension persists (calcium gluconate is acceptable but contains a lower concentration of Ca^{2+}).
- If hypotension persists despite calcium chloride infusion, a high-dose insulin and glucose infusion is indicated. An initial loading dose of 1U/kg of short-acting insulin with 100mL of 20% glucose, followed by a maintenance infusion of 0.5U/kg/h of short-acting insulin that can be titrated to keep the SBP >100mmHg. With this, a 10% glucose infusion should be given, as needed, to provide euglycaemia, and BMs checked every 15min in the first hour and at least every 30min thereafter. Often a 20mmol K^{+} infusion will be required every 4–8h, and if so, K^{+} should be checked at least 2-hourly while the insulin infusion is running. Be aware that glucose requirements will rise, as the effects of the drug wear off and insulin resistance decreases.
- In severe cases where hypotension is severe, Intralipid® has been used, with success in anecdotal cases. The standard dosing as for local anaesthetic toxicity is recommended in patients not responding to other treatment: 1.5mL/kg of 20% lipid emulsion over 1min as a loading dose, followed by 15mg/kg/h thereafter, to a maximum cumulative dose of 12mg/kg.
- If hypotension fails to respond to these steps, consider inotropes/vasopressors, based on the clinical picture, or physical support with a balloon pump or similar device.

Carbon monoxide

The most common sources are smoke inhalation, poorly maintained domestic gas appliances, and deliberate inhalation of car exhaust fumes. CO poisoning causes tissue hypoxia by two mechanisms. First, it interrupts electron transport in mitochondria. Second, it reduces O_2 delivery both by competing with O_2 for binding to Hb (its affinity for Hb is 220-fold that of O_2) and altering the shape of the HbO_2 dissociation curve (making it shift to the left).

Presentation

Carboxy-haemoglobin (COHb) levels correlate poorly with clinical features. In general, levels of COHb of <30% cause only headache and dizziness. Fifty to 60% produces syncope, tachypnoea, tachycardia, and fits. Levels of >60% cause an increasing risk of cardiorespiratory failure and death.

Complications

- These are the predictable result of local hypoxia. Sites at particular risk are: the CNS, affecting cerebral, cerebellar, or midbrain function with confusion and incoordination; the myocardium with ischaemia and infarction; skeletal muscle, causing rhabdomyolysis and myoglobinuria; and skin involvement ranging from erythema to severe blistering.
- Long-term exposure can result in parkinsonism, ataxia, personality change, poor memory, dementia, and peripheral neuropathy.

Management

- Ensure the patient is removed from the source; apply a tight-fitting face mask, and give 100% O_2 .
- An ABG should be taken. Although PaO_2 may be normal, it is important to measure the COHb concentration on a co-oximeter. NB Monitoring O_2 saturation with a *pulse oximeter* is *unhelpful*, since it will not distinguish HbO_2 and COHb (hence the apparent O_2 saturation will be falsely high).
- O_2 should be continued until COHb is <5%, which may take up to 20h.
- Check a 12-lead ECG, and continuously monitor the rhythm. Take blood for FBC, U&Es, CPK, and troponin in symptomatic patients.
- If the patient is comatose, they should be intubated and ventilated with 100% FiO_2 (this reduces the half-life of COHb to 80min, compared to 320min on room air). This should also be considered in all patients who are severely acidotic or show evidence of myocardial ischaemia.
- Seizures should be controlled with IV diazepam (5–10mg).
- There is no evidence that hyperbaric O_2 improves outcome; it may be considered in those with severe poisoning (e.g. coma, neurological signs)—these patients should be discussed with the NPIS.
- If the patient has been exposed to CO in a house fire, consider whether they may have effects of soot inhalation or cyanide exposure.
- Ensure medical follow-up, as the neuropsychiatric sequelae may take many weeks to evolve.

Cyanide

Poisoning is most commonly seen in victims of smoke inhalation [hydrogen cyanide (HCN) is a combustion product of polyurethane foams]. Cyanide derivatives are, however, widely employed in industrial processes, and significant cyanide poisoning can occur in industrial accidents. Cyanide acts by irreversibly blocking mitochondrial electron transport.

Presentation

HCN gas can lead to cardiorespiratory arrest and death within a few minutes. Onset of effects after ingestion or skin contamination is generally much slower (up to several minutes or even hours). Note that the detection of the smell of bitter almonds is unhelpful.

Decisions regarding treatment are generally based on whether the patient is classified as having features of mild, moderate, or severe poisoning:

- *Mild*: nausea, dizziness, hyperventilation, and a lactate level of $<10\text{mmol/L}$.
- *Moderate*: reduced GCS scores or convulsions, vomiting, hypotension, a lactate level of $10\text{--}15\text{mmol/L}$.
- *Severe*: coma, fixed dilated pupils, cyanosis, cardiovascular instability or respiratory failure, a lactate level of $>15\text{mmol/L}$.

Prognostic features

- Ingestion of a few hundred milligrams of a cyanide salt is usually fatal in adults. Absorption can be delayed by a full stomach and high gastric pH (e.g. antacids).
- Patients surviving to reach hospital after inhalation of HCN are unlikely to have suffered significant poisoning.

Management

- Do *not* attempt mouth-to-mouth resuscitation. Give 100% O_2 by a tight-fitting face mask or ventilate via an ETT if necessary.
- Establish IV access.
- Check ABGs. Lactic acidosis indicates severe poisoning.
- Skin contamination requires thorough washing of the affected area with soap and water.
- All cases of suspected cyanide poisoning should be discussed with a poisons service or a clinical toxicologist before treatment.
- If mild features are present, then sodium thiosulfate can be used (25mL of 50% sodium thiosulfate over 10 min).
- In moderate toxicity, sodium thiosulfate can also be given at the dose above, with sodium nitrite (10mL of a 3% solution over 5–20min) or hydroxocobalamin (5g over 15min).
- In severe toxicity, dicobalt edetate or hydroxocobalamin are recommended if available. Dicobalt edetate is given at a dose of 300mg of Kelocyanor® IV over 1min, followed immediately by 50mL of 50% glucose; dicobalt edetate can be very toxic and potentially fatal if cyanide is not present.
- A second dose of dicobalt edetate can be given if no response to the first, but further doses can cause cobalt toxicity if the diagnosis is incorrect. Alternatively, give sodium nitrite (10mL of a 3% solution over 5–20min) and sodium thiosulfate (25mL of 50% solution). Methaemoglobin levels should be measured if sodium nitrite is given.

Digoxin

Presentation

- Nausea, vomiting, confusion, and diarrhoea.
- Visual disturbance (blurring, flashes, disturbed colour vision).
- Cardiac dysrhythmias (tachyarrhythmias or bradyarrhythmias), hypotension.

Complications

- Hyperkalaemia.
- Cardiac dysrhythmias—any type of brady- or tachyarrhythmias can occur in digoxin toxicity.

Management

- Take blood for a digoxin concentration (in patients not normally on digoxin, this should be at least 6h post-ingestion) and U&Es.
- Baseline 12-lead ECG and continuous ECG monitoring.
- Activated charcoal should be given if the patient presents within 1h of OD. Activated charcoal (25g) may be *repeated* every 2h, provided the patient is not vomiting.
- Sinus bradyarrhythmias and AV block usually respond to atropine (0.6mg IV, repeated to a total of 2.4mg). Asymptomatic ventricular ectopics do not require specific treatment.
- If hyperkalaemia is present, treat in the first instance with insulin and glucose, but a K^+ level of >6.5 is an indication for antibody treatment. Do not give calcium gluconate or chloride, as the increase in intracellular Ca^{2+} can provoke arrhythmias and worsen digoxin-related hypotension.
- Ventricular tachyarrhythmias should be treated with magnesium sulfate (8–10mmol IV).
- Indications for DigiFab® include haemodynamic instability, resistant ventricular tachyarrhythmias, or high K^+ levels requiring treatment with digoxin-binding antibody fragments (see Box 14.1).
- The neutralizing dose for patients intoxicated during chronic therapy is: (number of vials) = digoxin level (ng/mL) $\times$ weight (kg) $\times$ 0.01. Half this dose should initially be given, and repeated if there is recurrence of toxicity. Clinical effects, e.g. termination of VT, will take around 20–30min to occur. K^+ and free serum digoxin levels should be monitored for 24h after DigiFab® therapy, but be aware that often the levels will rise, as most assays will measure both bound and free digoxin levels. In patients with renal impairment, this rebound is delayed and monitoring should be extended to 72h.
- Generally, pacing is best avoided, owing to the excitable myocardium being more prone to arrhythmias, but if DigiFab® is not available, then a transvenous pacing wire or overdrive pacing may be the only option available.

Box 14.1 Indications for digoxin-specific antibodies

- K^+ levels of >6.5 .
- Severe bradyarrhythmias.
- Life-threatening tachyarrhythmias.

It is acceptable to treat hyperkalaemia with insulin and glucose, while digoxin-specific antibodies are sought.

Ethanol: acute intoxication

Patients may present either with acute intoxication, withdrawal syndromes, nutritional deficiency syndromes, or chronic toxicity (liver, CNS, peripheral neuromyopathy, etc.).

Presentation

Alcohol intoxication results in disinhibition, euphoria, incoordination, ataxia, stupor, and coma. Chronic alcoholics require higher blood ethanol levels than 'social' drinkers for intoxication. Obtain a history from friends or relatives. Examine the patient for signs of chronic liver disease, trauma, or signs of infection.

Complications

- Acute gastritis causes nausea and vomiting, abdominal pain, and GI bleeding.
- Respiratory depression and arrest, inhalation of vomit (with ARDS), and hypothermia may accompany profound sedation.
- Hypoglycaemia is common and should be excluded.
- Alcoholic ketoacidosis.
- Accidental injury, particularly head injury (subdural).
- Rhabdomyolysis and ARF.
- Infection (septicaemia, meningitis).

Management

- Mild to moderate intoxication usually requires no specific treatment—the need for admission for rehydration and observation depends on the individual patient. Admit all patients with stupor or coma.
- Check the airway is clear of vomitus and the patient is able to protect their airway. Nurse in the recovery position.
- Gastric lavage or charcoal are not indicated.
- Take blood for U&Es, CPK, glucose, and amylase, and consider ethanol levels and an ABG (acidosis). Consider the possibility of other drug OD.
- Monitor closely for respiratory depression, hypoxia, hypotension, and withdrawal syndromes (➡ Acute alcohol withdrawal, pp. 436–7; ➡ Acute alcohol withdrawal, pp. 718–19).
- Check blood glucose. In comatose patients with hypoglycaemia, give 25–50mL of 50% glucose, followed by an IVI of 10% glucose if necessary. The only concern is that glucose may precipitate WE in malnourished individuals. Therefore, ideally give a bolus of thiamine 1–2mg/kg IV before glucose.
- Rehydrate with IV fluids (avoid excessive use of saline in patients with signs of chronic liver disease); monitor urine output.
- Rarely, haemodialysis is used if intoxication is very severe or in the presence of acidosis.
- After recovery from the acute episode, arrange for a psychiatric or medical assessment and follow-up and referral to an alcohol rehabilitation programme if appropriate.
- For alcohol withdrawal and DT, see ➡ Acute alcohol withdrawal, pp. 436–7; ➡ Acute alcohol withdrawal, pp. 718–19.

Hypoglycaemic agents

Insulin

Insulin poisoning is an important cause of hypoglycaemia that may be deliberate or accidental, and can result in life-threatening consequences and be prolonged with long-acting insulin. If ingested, insulin is non-toxic.

Presentation

- Symptoms related to hypoglycaemia may present within 2h of injection: nausea, vomiting, diaphoresis, tachycardia, palpitations, agitation, and confusion related to cerebral oedema, followed by seizures and coma.
- Electrolyte abnormalities may include low K^+ , Mg^{2+} , and PO_4^{3-} .

Practice points

Watch out for those on β -blockers that may present with minimal symptoms of hypoglycaemia.

Management

- Airway, breathing, and circulation if severe hypoglycaemia!
- Correct any hypoglycaemia rapidly with 50mL of 50% glucose/100mL of 20% glucose or oral agents if alert.
- Commence a 10% glucose infusion, titrated to blood sugar levels, to continue thereafter.
- *Monitor:* U&Es, ECG, lab glucose at least hourly, and capillary glucose every 10–15min initially.
- Patients need to be observed for 6h after cessation of any glucose infusion to ensure their glucose levels remain normal prior to discharge.

Metformin

Biguanide hypoglycaemic agents may cause type B lactic acidosis that is mild at therapeutic doses but can be severe if taken in OD and/or in elderly patients with renal impairment.

Presentation

- Hypoglycaemia is uncommon but may occur.
- Abdominal pain, diarrhoea, and lactic acidosis may cause hyperventilation, $\downarrow$ GCS scores, and hypotension.

Management

- Consider *activated charcoal* (50g) if the patient presents within 1h.
- *Monitor:* U&Es, glucose, and venous bicarbonate.
- ABG in symptomatic patients. Any severe metabolic acidosis should be corrected with 8.4% sodium bicarbonate.
- *Haemodialysis:* is the treatment of choice for persistent metabolic acidosis and lactate levels consistently >10 , especially if poor renal function.

Sulfonylureas, e.g. gliclazide, glibenclamide, glimepiride, glipizide, tolbutamide

Sulfonylureas are very different in OD to biguanides, with a much higher likelihood of hypoglycaemia. Peak plasma concentrations occur at 4h in normal preparations and 12h in sustained-release preparations.

Presentation

- Hypoglycaemia is the most common serious presentation: nausea, vomiting, diaphoresis, tachycardia, palpitations, agitation, and confusion related to cerebral oedema, followed by seizures and coma.

Complications

- Cerebral oedema and seizures.
- ARF.

Management

- Airway, breathing, and circulation if severe hypoglycaemia!
- Correct any hypoglycaemia rapidly with 50mL of 50% glucose/100mL of 20% glucose or oral agents if alert.
- Commence a 10% glucose infusion, titrated to blood sugar levels, to continue thereafter.
- Consider *activated charcoal* (50g) if the patient presents within 1h.
- *Monitor*: U&Es, ECG, lab glucose hourly, and capillary glucose at least every 10–15min initially.
- If symptomatic, monitor for at least 12h and for 6h if asymptomatic.
- Octreotide IV should be used in patients with recurrent hypoglycaemia. The recommended doses in adults are 50 micrograms SC or IV, followed by three further doses 6h apart.

Iron

- The toxicity of a given iron preparation is dependent upon the proportion of elemental iron contained within it.
- Greater than 20mg/kg of elemental iron is likely to cause toxicity, while >200mg/kg may prove fatal.
- The early clinical features of iron toxicity are due to the corrosive effects of iron, while the late effects are the result of disruption to intracellular processes.

Presentation

- *Early (30min onwards):* vomiting, diarrhoea $\pm$ haematemesis and melaena, abdominal pain
- *Mid-latent phase (~6–12h):* the initial symptoms abate, and the patient can deceptively appear to be improving.
- *Late (from 12–48h):* there might be a return of the initial symptoms, together with hypotension, metabolic acidosis, evidence of hepatocellular necrosis, including hypoglycaemia, jaundice, encephalopathy, and coagulopathy. Respiratory and renal failure may also occur.
- *Very late (2–5 weeks):* scarring from the initial corrosive effects of iron can cause pyloric stenosis and small bowel strictures.

Investigations

- A serum iron level should be taken at 4h post-ingestion, if possible, along with FBC, U&Es, LFTs, glucose, and clotting.
- If a sustained-release preparation has been taken, then a further iron level should be taken at 6–8h.
- An ABG should be done if a significant OD is suspected.
- A *plain* AXR may be useful to assess the number of tablets ingested.

Management

- Give IV fluids and blood, as needed, but be careful not to fluid-overload these patients.
- There is no place for activated charcoal in the management of these patients, but whole bowel irrigation should be undertaken if sustained-release tablets have been taken or tablets can be seen within the stomach on X-ray.
- *Parenteral chelation therapy:* is indicated if the serum iron level is >90micromol/L (5mg/L) or in patients who are shocked, convulsing, or comatose.
- Give desferrioxamine IV initially at a rate of 15mg/kg/h. The generally recommended maximum daily dose is 80mg/kg; however, higher doses may be used in patients with severe poisoning—discuss with a poisons centre or a clinical toxicologist. Desferrioxamine may cause hypotension if infused more rapidly than recommended. Pulmonary oedema and ARDS have been reported in patients treated at >80mg/kg/day for >24h.

Lithium

Lithium has a low therapeutic index and is available in sustained-release (most commonly) and non-sustained-release preparations. It is very important to distinguish between acute, acute-on-chronic, and chronic toxicity, as they are distinct clinical entities.

Clinical classification of lithium toxicity

Acute toxicity occurs in the context of an acute OD of lithium; lithium OD in patients who are lithium-naïve is generally better tolerated than lithium OD in those who take lithium therapeutically (acute-on-chronic OD).

Chronic toxicity tends to occur if there has been impairment of renal function, dehydration, Na^+ depletion, or in the context of drug interactions with other drugs, e.g. ACEIs, NSAIDs, or diuretics.

There is a greater risk of neurological features and permanent impairment in patients with chronic toxicity (➡ see Management, pp. 762–3), and serum concentrations often correlate poorly with clinical features.

Presentation

- Thirst, polyuria, diarrhoea, vomiting, and fine tremor are common.
- In severe toxicity, the effects on the CNS generally predominate, with impairment of consciousness, confusion, coarse tremor, choreo-athetoid movements, urinary/faecal incontinence, hypertonia, and seizures.
- Non-neurological features seen in severe poisoning include hypernatraemia, cardiac arrhythmias, and hypotension.

Prognostic features

Features of toxicity are usually associated with lithium concentrations $>4\text{--}6\text{mmol/L}$ in acute lithium OD but can be seen at lower concentrations ($2\text{--}4\text{mmol/L}$) in acute-on-chronic OD or chronic accumulation; however, generally, clinical features are a more important prognostic marker than lithium concentrations.

Management

- If slow-release preparations are involved in a significant acute or acute-on-chronic OD, whole bowel irrigation with polyethylene glycol is useful. (NB Activated charcoal does not adsorb lithium).
- Check serum lithium concentration at 6h, and repeat 6- to 12-hourly (ensure the tube used does not contain lithium-heparin anticoagulant).
- Patients with slow-release lithium OD should be observed for 24h.
- Symptomatic patients should have an ECG.
- Check U&Es.
- Any diuretic (especially thiazides) or other drug likely to alter renal handling of lithium (e.g. NSAIDs) should be stopped.
- Correct any fluid or electrolyte deficits, and ensure adequate hydration. Forced diuresis should *not* be undertaken.

- Patients on chronic lithium therapy with concentrations $>4\text{mmol/L}$, particularly if they have neurological features, should be considered for haemodialysis; haemofiltration is an alternative but will need to be continued for at least 24h. Acute lithium toxicity less commonly results in severe toxicity requiring haemodialysis, but patients with serum lithium concentrations $>8\text{mmol/L}$ associated with neurological features may require haemodialysis.
- There is the potential for lithium rebound from tissue stores after haemodialysis. Lithium concentrations should be repeated 6- to 12-hourly, and patients should be observed for 24h after the end of haemodialysis/filtration.

Non-steroidal anti-inflammatory drugs

Ibuprofen, naproxen, diclofenac, indometacin, mefenamic acid, and piroxicam

Unless the ingestion is large, ingestion of NSAIDs is typically benign. Ibuprofen is one of the most common agents taken in OD; clinical features are unlikely at doses $<100\text{mg/kg}$.

Presentation

- GI effects are most common: nausea, vomiting, epigastric pain, and occasionally diarrhoea.
- Tinnitus, headache, and GI bleeding can occur but are rare.
- In large ODs, CNS effects—drowsiness, nystagmus, ataxia, blurred vision, disorientation, and coma can occur.
- Convulsions may occur, especially in ODs with mefenamic acid that lowers the seizure threshold.

Complications

- AKI.
- Metabolic acidosis.
- Exacerbation of asthma is a possibility.

Management

- Consider activated charcoal (50g) if the patient presents within 1h and $>100\text{mg/kg}$ of ibuprofen or >10 tablets of other non-steroidals have been taken.
- Patients should be observed for 4h if a potentially toxic dose has been consumed or 8h after sustained-release preparations.
- FBC, U&Es, and LFTs should be measured in large ingestions.
- Seizures are usually brief and rarely require specific treatment other than airway protection; if prolonged, diazepam 5–10mg IV should be used.
- Consider a PPI if significant GI irritation.

Recreational drugs: stimulants

Broadly, recreational drugs can be divided into stimulants, hallucinogens, and depressants.

Examples of stimulants: amphetamines (e.g. amphetamine, MDMA (3,4-methylenedioxymethamphetamine), methamphetamine), cocaine, piperazines, cathinones (e.g. mephedrone).

Amphetamines have been taken around the world for decades, but recently there has been a new wave of substituted amphetamines and phenylethylamines known as novel psychoactive substances (NPS), in particular the cathinones which are β -keto derivatives of amphetamine. A number of cathinones are used recreationally, including mephedrone, methedrone, and methylone. Other NPS stimulants include indanes, tetralines, pipradrols, and benofurans.

Common complications of stimulants include:

- Tachycardia, hypertension, and cardiac arrhythmias, often SVTs.
- Central effects (most relating to $\uparrow$ sympathetic nervous system stimulation): sweating, tremor, bruxism, mydriasis, seizures, psychomotor agitation, anxiety, psychosis, and delusions.
- A hyperthermic syndrome which has some similarity to serotonin syndrome: hyperthermia, hypertonia, nystagmus, clonus, autonomic instability which may result in rhabdomyolysis, DIC, and ARF.

Less common complications include cardiomyopathy (after chronic use), aortic dissection, and subarachnoid and intracerebral haemorrhage. Psychotic symptoms may persist once the acute phase has passed, and it is likely that chronic use is associated with a higher incidence of mental illness.

Cocaine

Cocaine may be used as cocaine powder (nasal insufflation or IV use) or as crack cocaine (smoked or IV injection). Many of the features of acute cocaine toxicity are similar to other stimulant recreational drugs (tachycardia, hypertension, psychomotor agitation); in addition, cocaine can cause ischaemic stroke, intracerebral haemorrhage, arrhythmias related to cardiac ion channel effects, and ACS.

Cocaine-related acute coronary syndrome and arrhythmias

- The mechanism of cocaine-related ACS (coronary artery vasoconstriction) is different to classical ACS, and therefore management is different.
- Na^+ channel and/or $\text{K}^+/\text{Ca}^{2+}$ channel blockade can result in broad complex tachyarrhythmias.

General management of stimulant toxicity

- Agitation may require diazepam (5–10mg IV initially); diazepam can also help with cocaine-related ACS by action on peripheral benzodiazepine receptors and coronary vasodilatation.
- Perform a 12-lead ECG for evidence of myocardial ischaemia (although the ECG is less sensitive in the setting of acute cocaine toxicity) or QRS/QTc prolongation (which indicates an $\uparrow$ risk of ventricular tachyarrhythmias).

- Narrow complex tachycardias: these generally settle with diazepam; rarely, DC cardioversion or verapamil (5–10mg IV) may be required.
- Significant hypertension (SBP >200mmHg, DBP >120mmHg) should be controlled initially with diazepam (5–10mg IV); if it is resistant to treatment with diazepam, start GTN (IVI of 1–2mg/min, titrating to response). β -blockers may worsen the hypertension through unopposed α effects.
- Hyperthermia (temperature of >39–40°C) should be treated with aggressive cooling (cold IV fluids, ice baths $\pm$ external cooling) and IV diazepam; if hyperthermia persists, further management with intubation and paralysis and more specific agents, such as dantrolene and/or cyproheptadine, should be considered; these cases should be discussed with a poisons centre and/or a clinical toxicologist. Rhabdomyolysis should be treated in the usual way (➡ Rhabdomyolysis, pp. 306–7).

Cocaine-specific management

- Chest pain should be treated with O₂, IV diazepam, and nitrates (SL or IV). If chest pain persists, coronary angiography should be considered to allow intraluminal therapy; if coronary angiography is not available, the patient should be discussed with a poisons centre and/or a clinical toxicologist, and other coronary vasodilators, such as verapamil or phentolamine, may be required.
- VT: treat with 1–2mL/kg of 8.4% sodium bicarbonate IV.

Recreational drugs: hallucinogens

Examples: LSD, ketamine, glaucine, tryptamines, phencyclidine, cannabis, mushrooms (*Psilocybe semilanceata*).

Ketamine

Usually used therapeutically as an anaesthetic and an analgesic. When used as a recreational drug of abuse, it is usually snorted or taken orally. Onset of effects is rapid, whatever method is used.

Presentation

- Vomiting, blurred vision, numbness, dizziness, and ataxia at low doses.
- Agitation, along with hallucinations and dissociation ('out-of-body experiences'), can be severe at moderate doses, together with mild tachycardia and hypertension.
- Rarely, at high doses, respiratory depression and pulmonary oedema can occur.

Magic mushrooms

The active ingredient is psilocybin, which is a 5-HT_{2A} receptor agonist.

Presentation

- Vomiting, flushing, dilated pupils, abdominal pain, visual and auditory hallucinations.
- Impairment of the ability to judge distances and height is common.
- Rarely, arrhythmias, MI, abnormal LFTs, and renal failure from rhabdomyolysis can occur.

General management of hallucinogenic toxicity

- The patient should be nursed in a calm environment.
- Monitor BP, HR, temperature, and RR every 30min.
- Diazepam is the treatment of choice for significant agitation.

Recreational drugs: depressants

Opioids

Opioid toxicity may occur as a result of opioid or opiate misuse, commonly heroin (taken IV, by skin-popping, smoked, or rarely snorted), or due to deliberate self-poisoning or supratherapeutic excess of opioids used as analgesics. It is important to remember that some opioids are present in combination formulations with paracetamol, and so there is the potential for paracetamol, in addition to opioid, toxicity. Some opioids, in particular methadone, are long-acting and the half-life is even more prolonged in OD.

Presentation

Pinpoint pupils and respiratory system and CNS depression leading to coma are typical. Both the RR and respiratory depth are ↓. The depressive effects are exacerbated by alcohol or other CNS depressants such as benzodiazepines. BP may be low, but significant hypotension is rare in pure opioid toxicity.

Prognostic features

- Non-cardiogenic pulmonary oedema carries a poor prognosis.
- Renal impairment reduces the elimination of many opiates and prolongs their duration of action.

Management

- Monitor RR, depth of respiration, and pulse oximetry. Give O₂ by mask.
- Establish IV access. If paracetamol–opioid combinations have been ingested, measure a plasma paracetamol concentration (➡ Paracetamol: assessment, p. 772).
- The specific antidote is naloxone (a pure opioid antagonist) which should be given IV in boluses of 0.2–0.4mg at 1–2min intervals in patients with respiratory depression/hypoxia until the patient has an RR >12/min and adequate respiratory depth/O₂ saturations. Avoid giving sufficient naloxone to completely reverse the effect of opiates in an opioid-dependent subject. This is likely to precipitate an acute withdrawal reaction. The end-point of naloxone therapy is adequate respiration.
- Doses of up to 2mg (and above) may be required, but if no response is seen at this dose, then additional or alternative causes of the clinical picture should be considered.
- The duration of action of naloxone is shorter than many opioids, and so either repeated IV boluses of naloxone or a naloxone infusion should be started to avoid re-sedation (starting with two-thirds of the dose required to initially rouse the patient per hour and adjusting as necessary). In the case of OD with long-acting opiates, such as methadone, infusion of naloxone may be necessary for 48–72h.

Complications

- All opioids can cause non-cardiogenic pulmonary oedema, although it is most frequently seen with IV heroin.
- Rhabdomyolysis can occur in opioid-induced coma but is not common.
- IVDUs may develop right-sided endocarditis and septic PEs (several localized infiltrates on CXR).

Practice points

The respiratory depressant effects of buprenorphine are not fully reversed by naloxone, and mechanical ventilation may be required in severe cases.

Gamma-hydroxybutyric acid (GHB) and gamma-butyrolactone (GBL)

GBL is rapidly converted to GHB after ingestion. GHB acts at gamma-aminobutyric acid (GABA)_B receptors in the brain, causing stimulation, followed by drowsiness and, in large doses, seizures, hypoventilation, and unconsciousness. It acts synergistically with ethanol on the CNS, causing respiratory depression.

- GHB or 'G' (along with its precursors GBL and 1,4-BD) is used both as a stimulant and also in body-building, owing to beliefs that it enhances GH production.

Presentation

- The clinical effects of GHB usually appear within 30–60min and last 2–4h.
- There is a brief stimulatory effect or 'high', followed by sedation with associated respiratory depression. Deaths are rare and usually result from respiratory arrest in the prehospital environment.
- Bradycardia can occur, but hypotension is rare.
- Vomiting occurs commonly and, together with CNS depression, can lead to aspiration; up to 5–10% of patients with severe GHB/GBL toxicity develop seizures.

Management

- Patients who present with respiratory depression need observation for at least 4h, while the effects of the drugs wear off.
- All patients require a venous blood gas to ensure no acidosis, and an ECG.
- Occasionally, patients may require intubation, owing to respiratory acidosis related to a very low RR, particularly if vomiting or seizures are also present. Generally, these patients recover rapidly and self-extubation may be seen.

GHB/GBL withdrawal

Regular use of GHB/GBL leads to a physical dependency, with acute withdrawal on cessation of their use. The symptoms are similar to those of alcohol withdrawal, but typically more severe and neuropsychiatric symptoms, including psychosis and hallucinations, are common.

Management

- Patients should be nursed in a calm and supportive environment.
- Diazepam is the mainstay of treatment, with initial doses of 5–10mg. Sometimes, massive doses are needed (>100mg within 24h) and may still not control symptoms, necessitating the need for intubation.
- Baclofen is a GABA_B receptor agonist that has been used as an unlicensed therapy in withdrawal; however, there is limited evidence, and the patient should be discussed with a poisons centre and/or a clinical toxicologist before using baclofen.

Paracetamol: assessment

In therapeutic doses, only a minor fraction of paracetamol is metabolized to the reactive metabolite *N*-acetyl-*p*-benzoquinoneimine (NABQI), which is detoxified by conjugation with glutathione. In OD, the normal metabolic routes become saturated; therefore, an ↑ fraction is metabolized via the cytochrome P450 system to NABQI; hepatic glutathione stores become depleted, and NABQI results in hepatocellular toxicity.

Paracetamol OD can be divided into an acute single OD and a staggered OD in which the tablets are taken over 1h.

In September 2012, the Medicines and Healthcare Products Regulatory Agency (MHRA) issued changes to the assessment and treatment of paracetamol poisoning with the antidote acetylcysteine in the UK. There is now no risk stratification, and for patients with a single acute oral paracetamol OD, there is just a single treatment line on the paracetamol nomogram and staggered ODs should be treated at a threshold of 75mg/kg of paracetamol/day.

Presentation

- Apart from mild nausea, vomiting, and anorexia, patients presenting within 24h of ingestion are generally asymptomatic.
- Hepatic necrosis becomes apparent in 24–36h, with vomiting, right subchondral pain/tenderness, jaundice, acute liver failure, and hypoglycaemia/encephalopathy.
- Encephalopathy may worsen over the next 72h, and oliguria and renal failure can develop.
- Lactic acidosis: either <12h (very rare, in massive paracetamol ingestions) or late in association with acute liver failure.

Paracetamol: management

Single acute paracetamol overdoses

Early (<8h since paracetamol ingestion)

- Give *activated charcoal* 50g to patients presenting within 1h of a significant ($>150\text{mg/kg}$) ingestion.
- Assess the need for treatment with the antidote *acetylcysteine* by plotting the timed paracetamol concentration on the nomogram (see Fig. 14.1). Take U&Es, LFTs, and INR at the same time as the plasma paracetamol concentration.
- There is no need to start *acetylcysteine* before the 4h concentration is known, as long as a result is known and acted upon within 8h.
- If the paracetamol concentration is on the line or within 10% of the line, then it is advisable to treat with *acetylcysteine* (see Box 14.2).

Late (>8h since paracetamol ingestion)

- All patients with a significant OD of paracetamol ($>75\text{mg/kg}$) who present 8–24h after ingestion should be treated with *acetylcysteine* until levels are available.
- At presentation, take a plasma paracetamol concentration, along with U&Es, LFTs, and INR, and plot the paracetamol concentration on the nomogram. Continue *acetylcysteine* if the plasma paracetamol concentration is above or within 10% of the nomogram. *Acetylcysteine* can be stopped if the plasma paracetamol concentration is well below the nomogram. Beware of interpretation of plasma paracetamol concentrations in late-presenting patients ($>14\text{--}16\text{h}$), as the nomogram treatment concentration is at or below the laboratory limit of detection.
- If there is doubt about whether or not to continue *acetylcysteine*, discuss with a poisons centre or a clinical toxicologist.

Very late (>24–36h since paracetamol ingestion)

- If there is doubt about whether to treat or not, discuss the case with a poisons centre or a clinical toxicologist.
- Treatment with *acetylcysteine* should NOT be started, unless there is RUQ tenderness, jaundice, or clinical/biochemical evidence of liver impairment.
- Bloods, as listed above, should be sent, including a plasma paracetamol concentration.
- If paracetamol is detected, then there is the potential that there is an inaccuracy in the history, and a full course of *acetylcysteine* should be given.
- If the INR is >1.3 or the ALT is >3 times the upper limit of normal, *acetylcysteine* should be started.

Staggered paracetamol overdoses

- There is no place for plasma paracetamol concentrations in the risk assessment of staggered paracetamol ODs. The 2012 MHRA update on the management of paracetamol poisoning suggests that all staggered ODs with an ingestion of $>75\text{mg/kg}$ over a 24h period should be started on treatment.

Notes for all patients

- Mild anaphylactoid reactions to acetylcysteine, commonly including nausea and vomiting, flushing, and a rash, occur in 10–25% of patients. These generally settle by stopping the acetylcysteine infusion; if not, chlorphenamine can be used. Acetylcysteine should be restarted at the next infusion rate once the reaction settles. Steroids have *no* role in the management of acetylcysteine adverse reactions.
- Adverse reactions are more likely in those with low plasma paracetamol concentrations.
- Monitor glucose with blood glucose testing strips at least 6-hourly if liver function is deteriorating.
- All patients should have their U&Es, clotting, and LFTs measured after acetylcysteine. If the ALT has doubled since admission or INR is >1.3 , further acetylcysteine is required (at the same rate and dose as the third infusion).
- Management of *acute liver failure* is discussed under ➡ Acute liver failure: management, pp. 278–9, and indications for transplant are shown in Box 14.3.

Box 14.2 September 2012 paracetamol treatment guidelines

- There is now a single paracetamol concentration treatment line of 100mg/L for acute (non-staggered) oral paracetamol OD (see Fig. 14.1).
- All staggered paracetamol ODs and patients with significant therapeutic excess should be started on acetylcysteine immediately.
- The duration of the first infusion is now 1h, but doses are otherwise unchanged:
 - 150mg/kg in 200mL of 5% glucose over 1h, followed by
 - 50mg/kg in 500mL of 5% glucose over 4h, and finally
 - 100mg/kg in 1L of 5% glucose over 16h.
- Acetylcysteine is prescribed in weight-based bands in millilitres, rather than milligrams.

Box 14.3 Indications for consideration of liver transplantation by a specialist centre in paracetamol overdose

- Late acidosis (>36 h post-OD) with arterial pH <7.3

or

- PT >100 s

and

- Serum creatinine level >300 micromol/L

and

- Grade 3 encephalopathy
- Lactate >3.5 mmol/L on admission to liver unit or >3.0 mmol/L after fluid resuscitation.

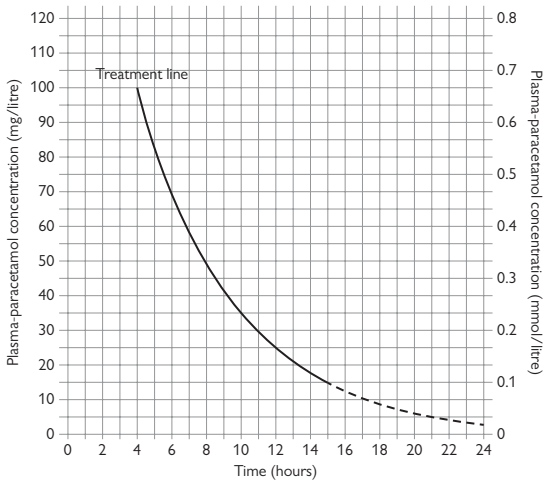


Fig. 14.1 Treatment for paracetamol overdoses. Measure plasma paracetamol concentrations at least 4h post-ingestion, and plot on the nomogram.

Reproduced from <https://www.gov.uk/drug-safety-update/treating-paracetamol-overdose-with-intravenous-acetylcysteine-new-guidance>. Contains public sector information licensed under the Open Government Licence v3.0.

Selective serotonin reuptake inhibitors

SSRIs include paroxetine, fluoxetine, citalopram, fluvoxamine, and sertraline. SSRIs are less toxic than tricyclic antidepressants in OD.

Presentation

- All SSRIs have similar toxic effects leading to sedation, nausea, vomiting, sinus tachycardia, and dilated pupils. More severe effects, such as ataxia, coma, convulsions, and ECG abnormalities (QT prolongation), are less common.
- Features of the 'serotonin syndrome' (e.g. hyperpyrexia, muscle rigidity, rhabdomyolysis) may occur in severe poisoning, particularly in patients who co-ingest another serotonergic agent.

Management

- Generally supportive care is all that is required.
- Consider oral activated charcoal (50g) in adults who have ingested >10 tablets in the past hour.
- Observe asymptomatic patients for at least 6h. Patients with ECG abnormalities should be observed until these resolve. Monitor pulse, BP, temperature, level of consciousness, and cardiac rhythm. Assess QRS and QTc durations.
- Correct hypotension by fluid challenge and raising the foot of the bed. Rarely, inotropes may be required.
- Control convulsions with IV diazepam (5–10mg in adults) or lorazepam (2–4mg in adults).

Serotonin syndrome

Many drugs can cause serotonin syndrome, including serotonin-releasing agents [e.g. SSRIs, e.g. paroxetine, fluoxetine, citalopram, sertraline; serotonin–noradrenaline reuptake inhibitors (SNRIs), e.g. venlafaxine, duloxetine; tricyclic antidepressants, e.g. clomipramine, imipramine; other medications with serotonergic activity, e.g. opioids (tramadol, fentanyl), St John's wort; recreational drugs such as MDMA (ecstasy) and cathinones; and MAOIs, e.g. phenelzine, tranylcypromine, moclobemide]. Serotonin syndrome is more likely when an individual is exposed to two agents which increase the serotonergic activity. Serotonin syndrome presents as a spectrum, from mild to potentially lethal, and may be associated with intentional self-poisoning and inadvertent drug interactions, but it can also occur with therapeutic use of serotonergic drugs.

Presentation

The majority of cases present within 24h (and most within 6h) of drug initiation or dose changes. Typically, a triad of mental status changes (agitation, confusion), autonomic hyperactivity (tachycardia, hypertension, hyperthermia), and neuromuscular excitation (clonus, hypertonia, hyper-reflexia) is seen. Severe rigidity and hyperthermia can be associated with significant complications, including rhabdomyolysis, AKI, metabolic acidosis, and DIC.

The *Hunter* criteria can be used to diagnose serotonin syndrome. To fulfil the criteria, a patient must have taken a serotonergic agent and have *one* of the following:

- Spontaneous clonus.
- Inducible clonus PLUS agitation or diaphoresis.
- Ocular clonus PLUS agitation or diaphoresis.
- Tremor PLUS hyper-reflexia.
- Hypertonia PLUS a temperature above 38°C PLUS ocular clonus or inducible clonus.

Investigations

Serotonin syndrome is a clinical diagnosis based on a typical clinical picture, together with a drug history of recent exposure to one or more serotonergic agents. Patients with significant serotonin syndrome, particularly those with hyperthermia, should have a CK level, clotting, U&Es, LFTs, and blood gas.

Differential diagnosis

- NMS:
 - Slower onset and resolution (days), extrapyramidal features with no clonus.
- Anticholinergic toxicity.
- Malignant hyperthermia.
- Sedative–hypnotic withdrawal.
- Meningitis/encephalitis.

Management

General supportive care

- Support the airway.
- Discontinuation of all serotonergic agents.
- IV crystalloid for volume replacement.
- Close monitoring of temperature, HR, and BP.
- Sedation with a benzodiazepine (e.g. IV lorazepam 2–4mg or PO diazepam 5–10mg in adults).

Hyperthermia

Severe hyperthermia can lead to rhabdomyolysis, AKI, metabolic acidosis, and DIC and should be aggressively managed with ice packs, cooling blankets, or invasive cooling devices. Consider paralysis and tracheal intubation if the temperature is $>40\text{--}41^{\circ}\text{C}$. If benzodiazepines and supportive care fail and the patient has ongoing hyperthermia, serotonin antagonists, such as cyproheptadine or chlorpromazine, can be considered (these patients should be discussed with a poisons centre or a clinical toxicologist, with critical care support).

Toxic alcohols

Ethylene glycol and methanol

Ethylene glycol is present in antifreeze and is rapidly absorbed from the gut. Peak concentrations occur 1–4h after ingestion. Ethylene glycol is metabolized to glycolaldehyde, then to glycolic, glyoxylic, and oxalic acids which are responsible for acidosis and the majority of the effects.

Methanol is metabolized to formaldehyde and then to formic acid which causes the characteristic blindness of toxicity.

The initial steps in the metabolism of both ethylene glycol and methanol are catalysed by alcohol dehydrogenase and can be blocked by competitive antagonism with ethanol or fomepizole.

Presentation

- Impaired consciousness ('inebriation' without alcohol on breath) in the early phase prior to metabolism of ethylene glycol/methanol.
- Nausea, vomiting, and abdominal pain may occur in the first few hours post-ingestion.
- Metabolic acidosis is usually delayed until 6–18h after ingestion. Initially, this is a non-lactic high-anion-gap metabolic acidosis.
- In methanol toxicity, visual symptoms present with falling visual acuity, photophobia, and the sensation of 'being in a snow storm'. Up to one-third of patients are left with permanent visual loss.
- CNS features, including seizures, are generally delayed by >24h and may signify the start of the development of severe features that can lead to coma and death.
- Oliguria suggestive of AKI typically occurs 24–48h post-ingestion.
- Late cranial neuropathies can be seen up to 20 days post-ingestion.

Prognostic features

- As little as 30mL of a toxic alcohol can be fatal in adults. However, toxic effects can be averted, even with massive ingestions, if specific treatment is started early.
- Co-ingestion of ethanol can actually be protective by blocking the metabolism of ethylene glycol/methanol to toxic metabolites.
- The degree of acidosis is the best indicator of a poor outcome. The presence of coma has also been shown to predict poor outcome.

Complications

- Severe metabolic acidosis.
- Oliguric renal failure.
- Cerebral oedema.
- Hypotension.
- Non-cardiogenic pulmonary oedema.
- Blindness (methanol).
- Convulsions.

Stages of ethylene glycol/methanol toxicity

Typically, after a brief period of inebriation due to the intoxicating effect of ethylene glycol/methanol itself, metabolic acidosis develops, followed by tachypnoea, coma, seizures, hypertension, the appearance of pulmonary infiltrates, and oliguric renal failure; blindness is also seen with methanol. Untreated, death from MOF occurs 24–36h after ingestion.

- **Stage 1** (30min to 12h after ingestion): appears intoxicated with alcohol (but no ethanol on breath), nausea and vomiting $\pm$ haematemesis. Metabolic acidosis develops.
- **Stage 2** (12–24h after ingestion): worsening metabolic acidosis, tachypnoea, sinus tachycardia, hypertension.
- **Stage 3** (24–72h after ingestion): AKI, hypocalcaemia in ethylene glycol poisoning (as a consequence of Ca^{2+} complexing with oxalate), blindness in methanol poisoning, convulsions, coma, severe acidosis, AKI, hypotension, pulmonary oedema.

Investigations

- Establish IV access. and take blood for U&Es, glucose, biochemical profile including Ca^{2+} , plasma osmolality, an ethanol concentration, and ethylene glycol/methanol concentrations where available.
- Check ABGs to assess the degree of acidaemia. Calculate the anion gap and osmolal gap. Patients will develop a high osmolal gap as they absorb the glycol over the first few hours. Thereafter, as the glycol is metabolized to acids, the osmolal gap will fall, while the patient's anion gap will climb and acidosis worsens.
- Interpret the osmolal gap with caution—a high osmolal gap increases the likelihood of a toxic alcohol ingestion; however, there are other causes of a high anion gap (e.g. sepsis) and toxic alcohol ingestion cannot be excluded by a low/normal osmolal gap.
- Microscope a fresh urine sample. Needle-shaped crystals of calcium oxalate monohydrate may be seen but are often a late feature, and their absence does not exclude ethylene glycol toxicity (they are *not* seen in methanol poisoning).

Management

- Delay in commencing treatment with an antidote will result in a more severely poisoned patient.
- Fomepizole is an inhibitor of alcohol dehydrogenase, and unlike ethanol, it does not cause CNS depression. It is expensive but easier to use than ethanol, and is the antidote of choice. It is given as a loading dose of 15mg/kg in 100mL of saline over 30min, followed by 12-hourly maintenance doses of 10mg/kg. If patients require haemodialysis or haemofiltration, increase the dose of fomepizole to 1mg/kg/h.

Indications for dialysis

- Severe, resistant acidosis, and/or AKI.

Tricyclic antidepressants

First-generation agents (e.g. amitriptyline, imipramine, and dosulepin) are the most likely to cause lethal intoxication. The newer second-generation tricyclics (e.g. lofepramine) and tetracyclics are generally much safer in OD.

Presentation

- Anticholinergic features are prominent early on, with dry mouth, dilated pupils, blurred vision, sinus tachycardia, urinary retention, myoclonic jerking, agitation, and hallucinations.
- Cardiac arrhythmias chiefly arise from the blockade of inactivated fast Na^+ channels in the heart. Hypotension can also occur as a result of α_1 adrenergic blockade and impaired cardiac contractility.
- Convulsions and coma with respiratory depression may precede the cardiac effects, and death can occur only a few hours after ingestion.
- Metabolic and respiratory acidosis can, in turn, worsen cardiotoxicity.

Complications

- Hypothermia, skin blistering (cf. barbiturates), and rhabdomyolysis are also reported.

Prognostic features

- Significant clinical features can be seen with ingestion of $>5\text{--}10\text{mg/kg}$.
- QRS prolongation is associated with an $\uparrow$ risk of convulsions and arrhythmias.

Management

- Patients with significant tricyclic antidepressant toxicity should be monitored closely in an ITU or a high-dependency area.
- Activated charcoal should be given PO (50g) within 1h.
- Record a 12-lead ECG, and monitor for a minimum of 6h post-ingestion.
- Alkalinization with boluses of 50mmol 8.4% sodium bicarbonate IV, aiming for an arterial pH of 7.45–7.55, is the initial treatment for patients with prolonged QRS duration, metabolic acidosis, hypotension, or arrhythmias.
- Severe hypotension may be treated with IV glucagon; inotropes or vasopressors may be required (➡ Hypovolaemic shock, p. 333).
- Control seizures with diazepam (5–10mg IV) in the first instance; the second-line treatment for seizures is phenobarbital.
- Arrhythmias should be treated with hypertonic sodium bicarbonate. Antiarrhythmics should be avoided.
- Tricyclic coma may last 24–48h. In some patients, recovery is marked by agitation and myoclonic jerks.

Practical procedures

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Arterial blood sampling

- An arterial blood sample is used to measure the arterial O_2 tension (PaO_2), CO_2 tension ($PaCO_2$), pH and bicarbonate/base excess levels, and Hb saturation (SaO_2).
- Familiarize yourself with the location and use of the blood gas machine. Arterial blood is obtained either by percutaneous needle puncture or from an indwelling arterial line.
- *Radial artery*: more accessible and more comfortable for the patient; best palpated between the bony head of the distal radius and the tendon of the flexor carpi radialis, with the wrist dorsiflexed. The Allen test is used to identify impaired collateral circulation in the hand (a contraindication to radial artery puncture)—the patient's hand is held high, with the fist clenched, and both the radial and ulnar arteries are compressed. The hand is lowered, the fist is opened, and the pressure from the ulnar artery is released. Colour should return to the hand within 5s.
- *Brachial artery*: best palpated medial to the biceps tendon in the antecubital fossa, with the arm extended and the palm facing up. The needle is inserted just above the elbow crease.
- *Femoral artery*: best palpated just below the midpoint of the inguinal ligament, with the leg extended. The needle is inserted below the inguinal ligament at a 90° angle.
- The chosen puncture site should be cleaned. Local anaesthetic should be infiltrated (not into the artery). Use one hand to palpate the artery, and the other hand to advance the heparin-coated syringe and needle (22–25G) at a 60 – 90° angle to the skin, with gentle aspiration. A flush of bright red blood indicates successful puncture. Remove about 2–3mL of blood; withdraw the needle, and ask an assistant to apply pressure to the puncture site for 5–15min. Air bubbles should be removed. The sample is placed on ice and analysed within 15min (to reduce O_2 consumption by WBC).
- *Complications*: include persistent bleeding, bruising, injury to the blood vessel, and local thrombosis.

Arterial line insertion 1

Indications

- Continuous monitoring of arterial BP in critically ill patients with haemodynamic instability.
- Repeated arterial blood sampling.

Contraindications

- Coagulopathy.
- Raynaud's phenomenon.
- Thromboangiitis obliterans.
- Advanced atherosclerosis.
- End-arteries, such as the brachial artery, should be avoided.

Initial measures

- Locate a palpable artery (e.g. radial or femoral).
- Assess the ulnar blood flow using the Allen test before inserting a radial line (➡ Arterial blood sampling, p. 784).
- Position the hand in moderate dorsiflexion, with the palm facing up (to bring the artery closer to the skin).
- The site should be cleaned with a sterile preparation solution and draped appropriately.
- Use sterile gloves.
- Use local anaesthetic (1% lidocaine) in a conscious patient.

Over-the-wire technique

(See Fig. 15.1.)

- Palpate the artery with the non-dominant hand (1–2cm from the wrist, between the bony head of the distal radius and the flexor carpi radialis tendon).
- The catheter and needle are advanced towards the artery at a 30–45° angle (see Fig. 15.1a) until blood return is seen (see Fig. 15.1b).
- The catheter and needle are then advanced through the vessel a few millimetres further (see Fig. 15.1c).
- The needle is removed (see Fig. 15.1d).
- The catheter is slowly withdrawn until pulsatile blood flow is seen (see Fig. 15.1e).
- When pulsatile blood flow is seen, the wire is advanced into the vessel (see Fig. 15.1f).
- The catheter is advanced further into the vessel *over the wire* (see Fig. 15.1g).
- While placing pressure over the artery, the wire is removed (see Fig. 15.1h) and the catheter is connected to a transduction system.
- Secure the catheter in place using suture or tape.
- Check perfusion to the hand after insertion of the arterial line and at frequent intervals.
- The line should be removed if there are any signs of vascular compromise or as early as possible after it is no longer needed.

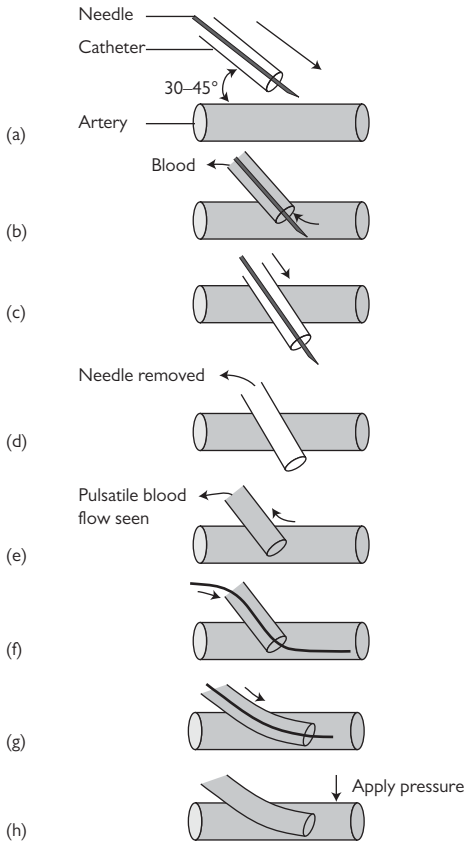


Fig. 15.1 Arterial line insertion: over-the-wire technique.

Arterial line insertion 2

Over-the-needle technique

(See Fig. 15.2.)

Locate and palpate the artery with the non-dominant hand (1–2cm from the wrist, between the bony head of the distal radius and the flexor carpi radialis tendon).

- The catheter and needle are advanced towards the artery at a 30–45° angle (see Fig. 15.2a) until blood return is seen (see Fig. 15.2b).
- The catheter and needle are then advanced slightly further, and the catheter/needle angle is lowered to 10–15° (see Fig. 15.2c).
- The catheter is advanced *over the needle* into the vessel (see Fig. 15.2d).
- Proximal pressure is applied to the artery; the needle is removed (see Fig. 15.2e) and the catheter is connected to a transduction system.
- Secure the catheter in place using suture or tape.
- Check perfusion to the hand after insertion of the arterial line and at frequent intervals.

Complications

- Local and systemic infection.
- Bleeding, haematoma, bruising.
- Vascular complications: blood vessel injury, pseudoaneurysm, thromboembolism, and vasospasm.
- Arterial spasm may occur after multiple unsuccessful attempts at arterial catheterization. If this occurs, use an alternative site.
- There may be difficulty in passing a wire or catheter, despite the return of pulsatile blood. Adjustment of the angle, withdrawal of the needle, or a slight advance may be helpful.

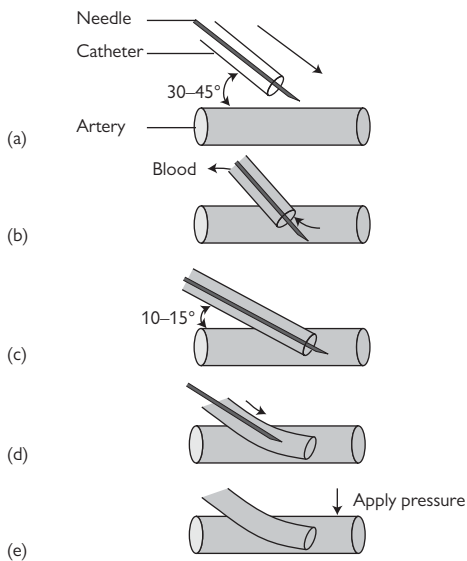


Fig. 15.2 Arterial line insertion: over-the-needle technique.

Central line insertion

You will need

- Sterile dressing pack, gloves, and sterile occlusive dressing.
- A 5- and 10-mL syringe, green (21G) and orange (25G) needles.
- Local anaesthetic (e.g. 2% lidocaine), saline flush.
- Central line (e.g. 16G long Abbocath® or Seldinger catheter).
- Silk suture and needle, No. 11 scalpel blade.

Risks

- Arterial puncture (remove and apply local pressure).
- Pneumothorax (insert a chest drain or aspirate if required).
- Haemothorax or chylothorax (mainly left subclavian lines).
- Infection (local, septicaemia, bacterial endocarditis).
- Brachial plexus or cervical root damage (infiltration with local anaesthetic).
- Arrhythmias.

General procedure

- The basic technique is the same whatever vein is cannulated.
- Lie the patient supine ($\pm$ head-down tilt).
- Turn the patient's head away from the side you wish to use.
- Clean the skin with chlorhexidine: from the angle of the jaw to the clavicle for IJV cannulation, and from the midline to the axilla for the subclavian approach.
- Use drapes to isolate the sterile field.
- Flush the lumen of the central line with saline.
- Identify your landmarks (see Figs. 15.3 and 15.4).
- Infiltrate the skin and subcutaneous tissue with local anaesthetic.
- Have the introducer needle and the Seldinger guidewire within easy reach, so that you can reach them with one hand without having to release your other hand. Your fingers may be distorting the anatomy slightly, making access to the vein easier and, if released, it may prove difficult to relocate the vein.
- With the introducer needle in the vein, check that you can aspirate blood freely. Use the hand that was on the pulse to immobilize the needle relative to the skin.
- Remove the syringe and pass the guidewire into the vein; it should pass freely. If there is resistance, remove the wire; check that the needle is still within the lumen, and try again.
- Remove the needle, leaving the wire within the vein, and use a sterile swab to maintain gentle pressure over the site of venepuncture to prevent excessive bleeding.
- With a No. 11 blade, make a nick in the skin where the wire enters, to facilitate dilatation of the subcutaneous tissues. Pass the dilator over the wire and remove, leaving wire *in situ*.
- Pass the central line over the wire into the vein. Remove the guidewire; flush the lumen with fresh saline, and close to air.
- Suture the line in place, and cover the skin penetration site with a sterile occlusive dressing.
- Measuring the CVP (see Box 15.1).

Box 15.1 Measuring the CVP—tips and pitfalls

- When asked to see a patient at night on the wards with an abnormal CVP reading, it is a good habit to always recheck the zero and the reading yourself.
- Always do measurements with the mid-axillary point as the zero reference. Sitting the patient up will drop the central filling pressure (pooling in the veins).
- Fill the manometer line, being careful not to soak the cotton ball stop. If this gets wet, it limits the free-fall of saline or glucose in the manometer line.
- Look at the rate and character of the venous pressure. It should fall to its value quickly and swing with respiration.
- If it fails to fall quickly, consider whether the line is open (i.e. saline running in) or blocked with blood clot, positional (up against a vessel wall; ask the patient to take some deep breaths), or arterial blood (blood tracks back up the line). Raise the whole dripstand (if you are strong), and make sure that the level falls. If it falls when the whole stand is elevated, it may be that the CVP is very high.
- It is easier, and safer, to cannulate a central vein with the patient supine or head down. There is an ↑ risk of air embolus if the patient is semi-recumbent.

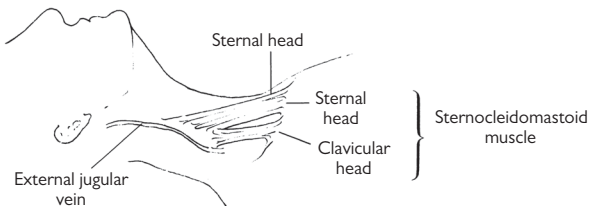
Internal jugular vein cannulation

The IJV runs just posterolateral to the carotid artery within the carotid sheath and lies medial to the sternocleidomastoid (SCM) in the upper part of the neck, between the two heads of the SCM in its medial portion, and enters the subclavian vein (SCV) near the medial border of the anterior scalene muscle (see Fig. 15.3a). There are three basic approaches to IJV cannulation: medial to the SCM, between the two heads of the SCM, or lateral to the SCM. The approach used varies and depends on the experience of the operator and the institution.

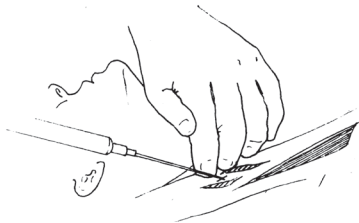
- Locate the carotid artery between the sternal and clavicular heads of the SCM at the level of the thyroid cartilage; the IJV lies just lateral and parallel to it.
- Keeping the fingers of one hand on the carotid pulsation, infiltrate the skin with local anaesthetic thoroughly, aiming just lateral to this and ensuring that you are not in a vein.
- Ideally, first locate the vein with a blue or green needle. Advance the needle at 45° to the skin, with gentle negative suction on the syringe, aiming for the ipsilateral nipple, lateral to the pulse.
- If you fail to find the vein, withdraw the needle slowly, maintaining negative suction on the syringe (you may have inadvertently transfixed the vein). Aim slightly more medially and try again.
- Once you have identified the position of the vein, change to the syringe with the introducer needle; cannulate the vein, and pass the guidewire into the vein (see Fig. 15.3).

Tips and pitfalls

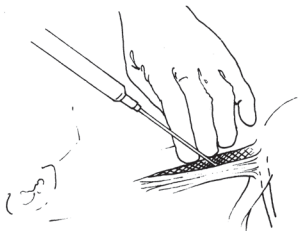
- Venous blood is dark, and arterial blood is pulsatile and bright red!
- Once you locate the vein, change to the syringe with the introducer needle, taking care not to release your fingers from the pulse; they may be distorting the anatomy slightly, making access to the vein easier and, if released, it may prove difficult to relocate the vein.
- The guidewire should pass freely down the needle and into the vein. With the left IJV approach, there are several acute bends that need to be negotiated. If the guidewire keeps passing down the wrong route, ask your assistant to hold the patient's arms out at 90° to the bed, or even above the patient's head, to coax the guidewire down the correct path.
- For patients who are intubated or requiring respiratory support, it may be difficult to access the head of the bed. The anterior approach may be easier (see Fig. 15.3b) and may be done from the side of the bed (the left side of the bed for right-handed operators, using the left hand to locate the pulse and the right to cannulate the vein).
- The IJV may also be readily cannulated with a long Abbocath®. No guidewire is necessary, but, as a result, misplacement is more common than with the Seldinger technique.
- When using an Abbocath®, on cannulating the vein, remember to advance the sheath and needle a few millimetres to allow the tip of the plastic sheath (~1mm behind the tip of the bevelled needle) to enter the vein. Holding the needle stationary, advance the sheath over it into the vein.
- Arrange for a CXR to confirm the position of the line.



(a) Surface anatomy of external and internal jugular veins



(b) Anterior approach: the chin is in the midline and the skin puncture is over the sternal head of the SCM muscle



(c) Central approach: the chin is turned away and the skin puncture is between the two heads of the SCM muscle

Fig. 15.3 Internal jugular vein cannulation.

Subclavian vein cannulation

The axillary vein becomes the SCV at the lateral border of the first rib and extends for 3–4cm just deep to the clavicle. It is joined by the ipsilateral IJV to become the brachiocephalic vein behind the sternoclavicular joint. The subclavian artery and brachial plexus lie posteriorly, separated from the vein by the scalenus anterior muscle. The phrenic nerve and the internal mammary artery lie behind the medial portion of the SCV and, on the left, lies the thoracic duct (see Fig. 15.4).

- Select the point 1cm below the junction of the medial third and middle third of the clavicle. If possible, place a bag of saline between the scapulae to extend the spine.
- Clean the skin with iodine or chlorhexidine.
- Infiltrate the skin and subcutaneous tissue and the periosteum of the inferior border of the clavicle with local anaesthetic up to the hilt of the green (21G) needle, ensuring that it is not in a vein.
- Insert the introducer needle with a 10-mL syringe, guiding gently under the clavicle. It is safest to initially hit the clavicle, and 'walk' the needle under it until the inferior border is just cleared. In this way, you keep the needle as superficial to the dome of the pleura as possible. Once it has skimmed underneath the clavicle, advance it slowly towards the contralateral sternoclavicular joint, aspirating as you advance. This technique minimizes the risk of pneumothorax, with high success.
- Once venous blood is obtained, rotate the bevel of the needle towards the heart. This encourages the guidewire to pass down the brachiocephalic vein, rather than up the IJV.
- The wire should pass easily into the vein. If there is difficulty, try advancing during the inspiratory and expiratory phases of the respiratory cycle.
- Once the guidewire is in place, remove the introducer needle, and make a small incision in the skin near the wire to allow the dilator to pass over the wire. When removing the dilator, note the direction that it faces; it should be slightly curved downwards. If it is slightly curved upwards, then it is likely that the wire has passed up into the IJV. When this happens, it is safer to remove the wire and start again.
- After removing the dilator, pass the central venous catheter over the guidewire; remove the guidewire, and secure.
- A CXR is mandatory after subclavian line insertion, to exclude a pneumothorax and to confirm satisfactory placement of the line, especially if fluoroscopy was not employed.

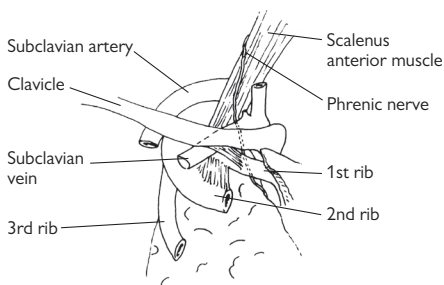


Fig. 15.4 The subclavian vein and surrounding structures.

Ultrasound-guided central venous catheterization 1

Traditional central venous catheterization methods rely on anatomical landmarks to predict vein position. However, the relationship between such landmarks and the vein position varies significantly in 'normal' individuals. Failure and complication rates using landmark methods are significant, and therefore serious complications may occur. Recent advances in portable US equipment have now made it possible to insert central venous catheters under 2D US guidance.

Advantages of this technique include:

- Identification of actual and relative vein positions.
- Identification of anatomical variations.
- Confirmation of target vein patency.

Guidelines from NICE (September 2002) state: 'Two-dimensional imaging ultrasound guidance is recommended as the preferred method for insertion of central venous catheters into the internal-jugular vein (IJV) in adults and children in elective situations'. However, training and equipment availability render such recommendations effectively useless in the UK at present.

Equipment/personnel needed

- Standard Seldinger-type kit or whatever is locally available.
- An assistant is essential.
- US equipment:
 - Screen: displays 2D US image of anatomical structures.
 - Sheaths: dedicated sterile sheaths of polyvinyl chloride (PVC) or latex long enough to cover the probe and connecting cable (a rubber band secures the sheath to the probe).
 - Probe: a transducer which emits and receives US information to be processed for display. Marked with an arrow or a notch for orientation.
 - Power: battery or mains.
 - Sterile gel: transmits US and provides a good interface between the patient and the probe.

Preparation

Perform a preliminary non-sterile scan to access each IJV for patency and size.

Patient

Sterile precautions should be taken, with the patient's head turned slightly away from the cannulation site. Head-down tilt (if tolerated) or leg elevation to increase filling and the size of the IJV. Ensure adequate drapes to maintain a sterile field.

Excessive head rotation or extension may decrease the diameter of the vein.

US equipment

- Ensure that the display can be seen.
- The sheath is opened (operator) and the gel squirted in (assistant). *A generous amount of gel ensures good contact and air-free coupling between the probe tip and the sheath. Too little may compromise the image quality.*
- The probe and connecting cable are lowered into the sheath (assistant), which is then unrolled along them (operator).
- A rubber band secures the sheath to the probe.
- The sheath over the probe tip is smoothed out (wrinkles will degrade the image quality).
- Apply liberal amounts of gel to the sheathed probe tip for good US transmission and ↑ patient comfort during movement.

Ultrasound-guided central venous catheterization 2

Scanning

The most popular scanning orientation for IJV central catheter placement is the transverse plane.

- Apply the probe tip *gently* to the neck, lateral to the carotid pulse, at the cricoid level, or in the sternomastoid–clavicular triangle.
- Keep the probe perpendicular at all times, with the tip flat against the skin.
- Orientate the probe so that movement to the left ensures that the display looks to the left (and vice versa). Probes are usually marked to help orientation. By convention, the mark should be to the patient's right (transverse plane) or to the head (longitudinal scan). The marked side appears on the screen as a bright dot.
- If the vessels are not immediately visible, keep the probe perpendicular and gently glide medially or laterally until found.

When moving the probe, watch the screen—not your hands.

After identification of the IJV

- Position the probe so that the IJV is shown at the display's horizontal midpoint.
- Keep the probe immobile.
- Direct the needle (bevel towards probe) caudally under the marked midpoint of the probe tip at $\sim 60^\circ$ to the skin.
- The needle bevel faces the probe to help direct the guidewire down the IJV later.
- Advance the needle towards the IJV.

Needle passage causes a 'wavefront' of tissue compression. This is used to judge the progress of the needle and position. Absence of visible tissue reaction indicates incorrect needle placement. Just before vessel entry, 'tenting' of the vein is usually observed.

One of the most difficult aspects to learn initially is the steep needle angulation required, but this ensures that the needle enters the IJV in the US beam and takes the shortest and most direct route through the tissues.

Needle pressure may oppose vein walls, resulting in vein transfixion. Slow withdrawal of the needle with continuous aspiration can help result in lumen access.

Pass the guidewire into the jugular vein in the usual fashion.

Re-angling the needle from 60° to a shallower angle, e.g. 45° , may help guidewire feeding. Scanning the vein in the longitudinal plane may demonstrate the catheter in the vessel, but after securing and dressing the central venous catheter, an X-ray should still be obtained to confirm the central venous catheter position and exclude pneumothorax.

The most common error in measurement of the CVP, particularly in CVP lines which have been in place for some time, is due to partial or complete line blockade. With the manometer connected, ensure that the line is free-flowing; minor blockages can be removed by squeezing the rubber bung, with the line proximal being obliterated by acute angulation (i.e. bend the tube proximal). Measure the CVP at the mid-axillary line, with the patient supine. CVP falls with upright or semi-upright recumbency, regardless of the reference point. If the CVP is high, lift the stand that holds the manometer so that the apparent CVP falls by 10cm or so, and re-place the CVP stand to ground level. If the saline or manometer reading rises to the same level, then the CVP reading is accurate. In other words, one ensures that the CVP manometer level both falls and rises to the same level.

Pulmonary artery catheterization 1

Indications

PA catheters (Swan–Ganz catheters) allow direct measurement of a number of haemodynamic parameters that aid clinical decision-making in critically ill patients (evaluate RV and LV function, guide treatment, and provide prognostic information). The catheter itself has no therapeutic benefit, and there have been a number of studies showing ↑ mortality (and morbidity) with their use. Consider inserting a PA catheter in any critically ill patient, after discussion with an experienced physician, if the measurements will influence decisions on therapy (and not just to reassure yourself). Careful and frequent clinical assessment of the patient should always accompany measurements, and PA catheterization should not delay treatment of the patient.

General indications (not a comprehensive list) include:

- Management of complicated MI.
- Assessment and management of shock.
- Assessment and management of respiratory distress (cardiogenic versus non-cardiogenic pulmonary oedema).
- Evaluating effects of treatment in unstable patients (e.g. inotropes, vasodilators, mechanical ventilation, etc.).
- Delivering therapy (e.g. thrombolysis for PE, epoprostenol for pulmonary hypertension, etc.).
- Assessment of fluid requirements in critically ill patients.

Equipment required

- Full resuscitation facilities should be available, and the patient's ECG should be continuously monitored.
- Bag of heparinized saline for flushing the catheter and a transducer set for pressure monitoring. (Check that your assistant is experienced in setting up the transducer system *before* you start.)
- An 8F introducer kit (prepackaged kits contain the introducer sheath and all the equipment required for central venous cannulation).
- PA catheter: commonly a triple-lumen catheter, that allows simultaneous measurement of RA pressure (proximal port) and PA pressure (distal port) and incorporates a thermistor for measurement of cardiac output by thermodilution. Check your catheter before you start.
- Fluoroscopy is preferable, though not essential.

General technique

- Do not attempt this, unless you are experienced.
- Observe a strict aseptic technique using sterile drapes, etc.
- Insert the introducer sheath (at least 8F in size) into either the IJV or the SCV in the standard way. Flush the sheath with saline, and secure to the skin with sutures.
- Do not attach the plastic sterile expandable sheath to the introducer yet, but keep it sterile for use later once the catheter is in position (the catheter is easier to manipulate without the plastic covering).

- Flush all the lumens of the PA catheter, and attach the distal lumen to the pressure transducer. Check the transducer is zeroed (conventionally to the mid-axillary point). Check the integrity of the balloon by inflating it with the syringe provided (2mL of air), and then deflate the balloon.
- The procedure is detailed under ➤ Pulmonary artery catheterization 2, p. 802 and ➤ Pulmonary artery catheterization 3, p. 804.

(See Fig. 15.5.)

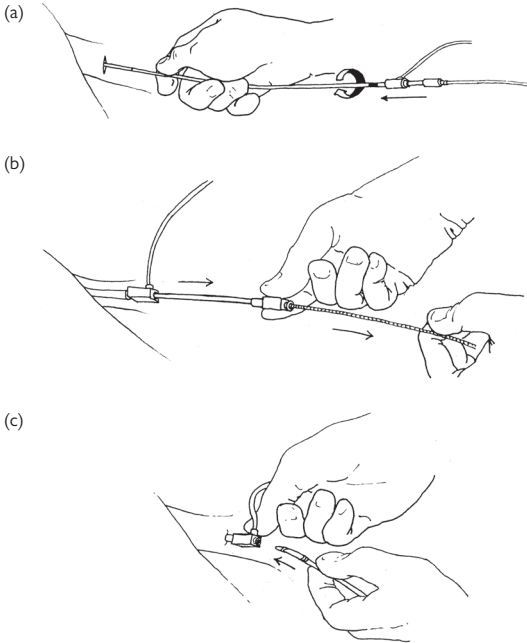


Fig. 15.5 Pulmonary artery catheterization. (a) The sheath and dilator are advanced into the vein over the guidewire. A twisting motion makes insertion easier. (b) The guidewire and dilator are then removed. The sheath has a haemostatic valve at the end, preventing leakage of blood. (c) The PA catheter is then inserted through the introducer sheath into the vein.

Pulmonary artery catheterization 2

Insertion technique

- Flush all the lumens of the PA catheter, and attach the distal lumen to the pressure transducer. Check the transducer is zeroed (conventionally to the mid-axillary point). Check the integrity of the balloon by inflating it with the syringe provided (~2mL of air), and then deflate the balloon.
- Pass the tip of the PA catheter through the plastic sheath, keeping the sheath compressed. The catheter is easier to manipulate without the sheath over it; once in position, extend the sheath over the catheter to keep it sterile.
- With the balloon deflated, advance the tip of the catheter to ~10–15cm from the right IJV or SCV, 15–20cm from the left (the markings on the side of the catheter are at 10cm intervals: two lines = 20cm). Check that the pressure tracing is typical of the RA pressure (see Fig. 15.6 and Table 15.1).
- Inflate the balloon and advance the catheter gently. The flow of blood will carry the balloon (and catheter) across the tricuspid valve, through the RV, and into the PA.
- Watch the ECG tracing closely, while the catheter is advanced. The catheter commonly triggers runs of VT when crossing the tricuspid valve and through the RV. VT is usually self-limiting but should not be ignored. Deflate the balloon, pull back, and try again.
- If >15cm of the catheter is advanced into the RV without the tip entering the PA, this suggests the catheter is coiling in the RV. Deflate the balloon, withdraw the catheter into the RA, reinflate the balloon, and try again using clockwise torque while advancing in the ventricle or flushing the catheter with cold saline to stiffen the plastic. If this fails repeatedly, try under fluoroscopic guidance.
- As the tip passes into a distal branch of the PA, the balloon will impact and not pass further; the wedge position and pressure tracing will change (see Fig. 15.6).
- Deflate the balloon, and check that a typical PA tracing is obtained. If not, try flushing the catheter lumen, and, if that fails, withdraw the catheter until the tip is within the PA, and begin again.
- Reinflate the balloon slowly. If the PCWP is seen before the balloon is fully inflated, it suggests the tip has migrated further into the artery. Deflate the balloon and withdraw the catheter 1–2cm, and try again.
- If the pressure tracing flattens and then continues to rise, you have 'overwedged'. Deflate the balloon, pull back the catheter 1–2cm, and start again.
- When a stable position has been achieved, extend the plastic sheath over the catheter and secure it to the introducer sheath. Clean any blood from the skin insertion site with antiseptic, and secure a coil of the PA catheter to the patient's chest to avoid inadvertent removal.
- Obtain a CXR to check the position of the catheter. The tip of the catheter should ideally be no more than 3–5cm from the midline.

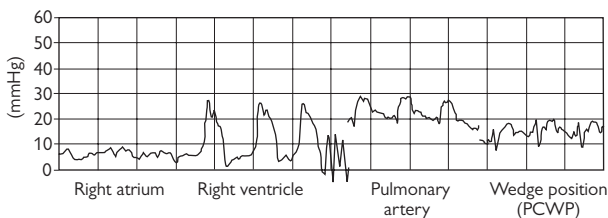


Fig. 15.6 Pressure tracings during pulmonary artery catheterization.

Table 15.1 Normal values of right heart pressures and flows

<i>Right atrial pressure</i>	0–8mmHg
<i>Right ventricle</i>	
Systolic	15–30mmHg
End diastolic	0–8mmHg
<i>Pulmonary artery</i>	
Systolic/diastolic	15–30/4–12mmHg
Mean	9–16mmHg
<i>Pulmonary capillary wedge pressure</i>	2–10mmHg
<i>Cardiac index</i>	2.8–4.2L/min/m ²

Pulmonary artery catheterization 3

Tips and pitfalls

- Never withdraw the catheter with the balloon inflated.
- Never advance the catheter with the balloon deflated.
- Never inject liquid into the balloon.
- Never leave the catheter with the balloon inflated, as pulmonary infarction may occur.
- The plastic of the catheter softens with time at body temperature, and the tip of the catheter may migrate further into the PA branch. If the pressure tracing with the balloon deflated is 'partially wedged' (and flushing the catheter does not improve this), withdraw the catheter 1–2cm and reposition.
- Sometimes it is impossible to obtain a wedged trace. In this situation, one has to use the PA diastolic pressure as a guide. In health, there is 72–4mmHg difference between the PA diastolic pressure and PCWP. Any condition which causes pulmonary hypertension (e.g. severe lung disease, ARDS, long-standing valvular disease) will alter this relationship.
- *Valvular lesions, VSDs, prosthetic valves, and pacemakers:* if these are present, then seek advice from a cardiologist. The risk of subacute bacterial endocarditis (SBE) may be sufficiently great that the placement of a PA catheter may be more detrimental than beneficial.
- PEEP (➡ Positive end-expiratory pressure, p. 831) measurement and interpretation if PCWP in patients on PEEP depends on the position of the catheter. Ensure the catheter is below the level of the LA on a lateral CXR. Removing PEEP during measurement causes marked fluctuations in haemodynamics and oxygenation, and the pressures do not reflect the state once back on the ventilator.

Complications

- *Arrhythmias:* watch the ECG tracing closely, while the catheter is advanced. The catheter commonly triggers runs of VT when crossing the tricuspid valve and through the RV. If this happens, deflate the balloon, pull back, and try again. VT is usually self-limiting but should not be ignored.
- *PA rupture* (~0.2% in one series): damage may occur if the balloon is overinflated in a small branch. Risk factors include MV disease (large v wave confused with poor wedging), pulmonary hypertension, multiple inflations, or hyperinflations of the balloon. Haemoptysis is an early sign. It is safer to follow PA diastolic pressures if these correlate with the PCWP.
- *Pulmonary infarction.*
- *Knots:* usually occur at the time of initial placement in patients where there has been difficulty in traversing the RV. Signs include loss of pressure tracing, persistent ectopy, and resistance to catheter manipulation. If this is suspected or has occurred, stop manipulation and seek expert help.
- *Infection:* risks increase with the length of time the catheter is left *in situ*. The pressure transducer may occasionally be a source of infection. Remove the catheter and introducer, and replace only if necessary.
- *Other complications:* complications associated with central line insertion, thrombosis and embolism, balloon rupture, and intracardiac damage.

Indications for temporary pacing

1 Following acute MI

- Asystole.
- Symptomatic CHB (any territory).
- Symptomatic secondary heart block (any territory).
- Trifascicular block:
 - Alternating LBBB and RBBB.
 - First-degree heart block + RBBB + left axis deviation.
 - New RBBB and left posterior hemiblock.
 - LBBB and long PR interval.
- After anterior MI:
 - Asymptomatic CHB.
 - Asymptomatic second-degree (Mobitz II) block.
- Symptomatic sinus bradycardia unresponsive to atropine.
- Recurrent VT for atrial or ventricular overdrive pacing.

2 Unrelated to MI

- Symptomatic sinus or junctional bradycardia unresponsive to atropine (e.g. carotid sinus hypersensitivity).
- Symptomatic secondary heart block or sinus arrest.
- Symptomatic CHB.
- Torsades de pointes tachycardia.
- Recurrent VT for atrial or ventricular overdrive pacing.
- Bradycardia-dependent tachycardia.
- Drug OD (e.g. verapamil, β -blockers, digoxin).
- Permanent pacemaker box change in a patient who is pacing-dependent.

3 Before general anaesthesia

- The same principles as for acute MI (see earlier).
- Sinoatrial disease and secondary (Wenckebach) heart block only need prophylactic pacing if there are symptoms of syncope or pre-syncope.
- CHB.

Transvenous temporary pacing

- The technique of temporary pacing is described on  Temporary cardiac pacing: ventricular pacing, pp. 808–9.
- The most commonly used pacing mode and the mode of choice for life-threatening bradyarrhythmias is ventricular demand pacing (VVI) with a single bipolar wire positioned in the RV (see  Temporary cardiac pacing: ventricular pacing, pp. 808–9 for an explanation of common pacing modes).
- In critically ill patients with impaired cardiac pump function and symptomatic bradycardia (especially with RV infarction), cardiac output may be $\uparrow$ by up to 20% by maintaining AV synchrony. This requires two pacing leads, one atrial and one ventricular, and a dual pacing box.

Epicardial temporary pacing

Following cardiac surgery, patients may have *epicardial wires* (attached to the pericardial surface of the heart) left in for up to 1 week in case of post-operative heart block or bradyarrhythmia. These may be used in the same way as the more familiar transvenous pacing wires, but the threshold may be higher.

AV sequential pacing

In critically ill patients with impaired cardiac pump function and symptomatic bradycardia (especially with RV infarction), cardiac output may be ↑ by up to 20% by maintaining AV synchrony. This requires two pacing leads, one atrial and one ventricular, and a dual pacing box.

Patients most likely to benefit from AV sequential pacing

- Acute MI (especially RV infarction).
- 'Stiff' LV (aortic stenosis, hypertrophic cardiomyopathy, hypertensive heart disease, amyloidosis).
- Low cardiac output states (cardiomyopathy).
- Recurrent atrial arrhythmias.

Temporary cardiac pacing: ventricular pacing

- *Cannulate a central vein:* the wire is easiest to manipulate via the right internal jugular (RIJ) approach but is more comfortable for the patient via the right SCV. The left internal jugular (LIJ) approach is best avoided, as there are many acute bends to negotiate and a stable position is difficult to achieve. Avoid the left subclavicular area, as this is the preferred area for permanent pacemaker insertion and should be kept 'virgin', if possible. The femoral vein may be used, but the risk of DVT and infection is high.
- *Insert a sheath:* (similar to that for PA catheterization) through which the pacing wire can be fed. Pacing wires are commonly 5F or 6F, and a sheath at least one size larger is necessary. Most commercially available pacing wires are prepacked with an introducer needle and a plastic cannula similar to an Abbocath® which may be used to position the pacing wire. However, the cannula does not have a haemostatic seal. The plastic cannula may be removed from the vein, leaving the bare wire entering the skin, once a stable position has been achieved. This reduces the risk of wire displacement but also makes repositioning of the wire more difficult, should this be necessary, and the infection risk is higher.
- Pass the wire through the sterile plastic cover that accompanies the introducer sheath, and advance into the upper RA (see Fig. 15.7), but do not unfurl the cover yet. The wire is much easier to manipulate with gloved hands, without the additional hindrance of the plastic cover.
- Advance the wire, with the tip pointing towards the RV; it may cross the tricuspid valve easily. If it fails to cross, point the tip to the lateral wall of the atrium and form a loop. Rotate the wire, and the loop should fall across the tricuspid valve into the ventricle.
- Advance and rotate the wire, so that the tip points inferiorly as close to the tip of the RV (laterally) as possible.
- If the wire does not rotate down to the apex easily, it may be because you are in the coronary sinus, rather than in the RV. (The tip of the wire points to the left shoulder.) Withdraw the wire, and re-cross the tricuspid valve.
- Leave some slack in the wire; the final appearance should be like the outline of a sock, with the 'heel' in the RA, the 'arch' over the tricuspid valve, and the 'big toe' at the tip of the RV.
- Connect the wire to the pacing box, and check the threshold. Ventricular pacing thresholds should be <1.0V, but a threshold of up to 1.5V is acceptable if another stable position cannot be achieved.
- Check for positional stability. With the box pacing at a rate higher than the intrinsic HR, ask the patient to take some deep breaths, cough forcefully, and sniff. Watch for failure of capture, and, if so, reposition the wire.
- Set the output to 3V and the box on 'demand'. If the patient is in sinus rhythm and has an adequate BP, set the box rate to just below the patient's rate. If there is CHB or bradycardia, set the rate at 70–80/min.

- Cover the wire with the plastic sheath, and suture the sheath and wire securely to the skin. Loop the rest of the wire, and fix to the patient's skin with adhesive dressing.
- When the patient returns to the ward, obtain a CXR to confirm satisfactory positioning of the wire and to exclude a pneumothorax.

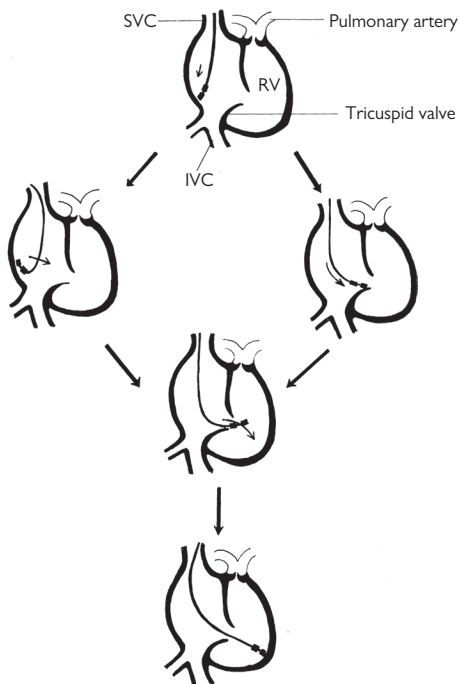


Fig. 15.7 Insertion of a ventricular pacing wire.

Temporary cardiac pacing: atrial pacing

(See Fig. 15.8.)

- The technique of inserting an atrial temporary wire is similar to that of ventricular pacing (⚡ Temporary cardiac pacing: ventricular pacing, pp. 808–9; see Box 15.2).
- Advance the atrial wire until the 'J' is reformed in the RA.
- Rotate the wire, and withdraw slightly to position the tip in the RA appendage. Aim for a threshold of $<1.5V$.
- If atrial wires are not available, a ventricular pacing wire may be manipulated into a similar position or passed into the coronary sinus for LA pacing.

Box 15.2 Checklist for pacing wire insertion

- Check the screening equipment and defibrillator work.
- Check the type of pacing wire—atrial wires have a preformed 'J' that allows easy placement in the atrium or appendage and is very difficult to manipulate into a satisfactory position in the ventricle.
- Ventricular pacing wires have a more open, gentle 'J'.
- Check the pacing box (single versus dual or sequential pacing box) and leads to attach to the wire(s). Familiarize yourself with the controls on the box—you may need to connect up in a hurry if the patient's intrinsic rhythm slows further.

Remember to don the lead apron before wearing the sterile gown, mask, and gloves.

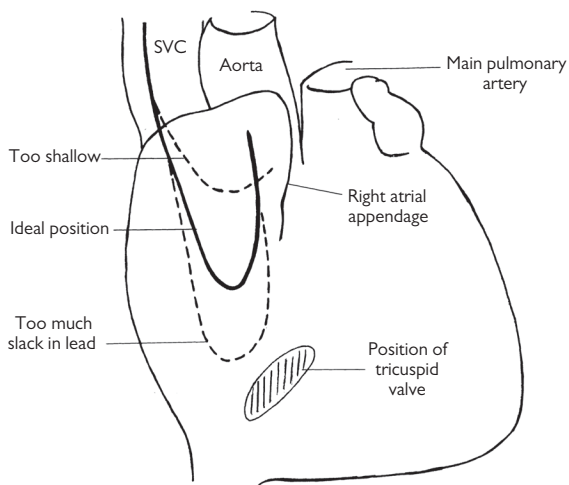


Fig. 15.8 Positioning an atrial wire for atrial pacing.

Temporary cardiac pacing: complications

(See Box 15.3.)

Ventricular ectopics or VT

- Non-sustained VT is common, as the wire crosses the tricuspid valve (especially in patients receiving an isoprenaline infusion), and does not require treatment.
- Try to avoid long runs of VT and, if necessary, withdraw the wire into the atrium and wait until the rhythm has settled.
- If ectopics persist after the wire is positioned, try adjusting the amount of slack in the wire in the region of the tricuspid valve (either more or less).
- Pacing the RVOT can provoke runs of VT.

Failure to pace and/or sense

- It is difficult to get low pacing thresholds ($<1.0V$) in patients with extensive MI (especially of the inferior wall) or cardiomyopathy or who have received class I antiarrhythmic drugs. Accept a slightly higher value if the position is otherwise stable and satisfactory.
- If the position of the wire appears satisfactory and yet the pacing thresholds are high, the wire may be in a left hepatic vein. Pull the wire back into the atrium and try again, looking specifically for ventricular ectopics as the wire crosses the tricuspid valve.
- The pacing threshold commonly doubles in the first few days due to endocardial oedema.
- If the pacemaker suddenly fails, the most common reason is usually wire displacement:
 - Increase the pacing output of the box.
 - Check all the connections of the wire and the battery of the box.
 - Try moving the patient to the left lateral position until arrangements can be made to reposition the wire.

Perforation

- A pericardial rub may be present in the absence of perforation (especially post-MI).
- *Presentation:* pericardial chest pain, increasing breathlessness, falling BP, enlarged cardiac silhouette on CXR, signs of cardiac tamponade, left diaphragmatic pacing at low output.
- *Management:*
 - If there are signs of cardiac tamponade, arrange for an urgent Echo and pericardial drainage (➡ Pericardial aspiration 1, pp. 814–15).
 - Reposition the wire.
 - Monitor the patient carefully with repeat Echos to detect incipient cardiac tamponade.

Diaphragmatic pacing

- High-output pacing (10V), even with a satisfactory position of the ventricular lead, may cause pacing of the left hemidiaphragm. At low voltages, this suggests perforation (see ➡ Perforation, p. 812).
- Right hemidiaphragm pacing may be seen with atrial pacing and stimulation of the right phrenic nerve.
- Reposition the wire if symptomatic (painful twitching, dyspnoea).

Box 15.3 Complications of temporary pacing

- Complications associated with central line insertion.
- Ventricular ectopics.
- Non-sustained VT.
- Perforation.
- Pericarditis.
- Diaphragmatic pacing.
- Infection.
- Pneumothorax.
- Cardiac tamponade.

Pericardial aspiration 1

Equipment

Establish peripheral venous access, and check that full facilities for resuscitation are available. Pre-prepared pericardiocentesis sets may be available. You will need:

- A trolley, as for central line insertion, with iodine or chlorhexidine for the skin, dressing pack, sterile drapes, local anaesthetic (lidocaine 2%), syringes (including a 50mL), needles (25G and 22G), a No. 11 blade, and silk sutures.
- Pericardiocentesis needle (15cm, 18G) or similar Wallace cannula.
- J-guidewire (≥ 80 cm, 0.035in diameter).
- Dilators (up to 7F).
- Pigtail catheter (≥ 60 cm with multiple sideholes, a large Seldinger-type CVP line can be used if no pigtail is available).
- Drainage bag and connectors.
- Facilities for fluoroscopy or echocardiographic screening.

Technique

(See Fig. 15.9.)

- Position the patient at $\sim 30^\circ$. This allows the effusion to pool inferiorly within the pericardium.
- Sedate the patient lightly with midazolam and fentanyl if necessary. Use with caution, as this may drop the BP in patients already compromised by the effusion.
- Put on a sterile gown and gloves; clean the skin from mid chest to mid abdomen, and place the sterile drapes on the patient.
- Infiltrate the skin and subcutaneous tissues with local anaesthetic, starting 1–1.5cm below the xiphisternum and just to the left of the midline, aiming for the left shoulder and staying as close to the inferior border of the rib cartilages as possible.
- The pericardiocentesis needle is introduced into the angle between the xiphisternum and the left costal margin, angled at $>30^\circ$. Advance slowly, aspirating gently and then injecting more lidocaine every few millimetres, aiming for the left shoulder.
- As the parietal pericardium is pierced, you may feel a 'give' and fluid will be aspirated. Remove the syringe, and introduce the guidewire through the needle.
- Check the position of the guidewire by screening. It should loop within the cardiac silhouette only and not advance into the SVC or PA.
- Remove the needle, leaving the wire in place. Enlarge the skin incision slightly, using the blade, and dilate the track.
- Insert the pigtail over the wire into the pericardial space, and remove the wire.
- Take specimens for microscopy, culture (and inoculate a sample into blood culture bottles), cytology, and haematocrit if bloodstained (an FBC tube; ask the haematologists to run on a Coulter counter for a rapid estimation of Hb).

- Aspirate to dryness, watching the patient carefully. Symptoms and haemodynamics (tachycardia) often start to improve with removal of as little as 100mL of pericardial fluid.
- If the fluid is heavily bloodstained, withdraw fluid cautiously; if the pigtail is in the RV, withdrawal of blood may cause cardiovascular collapse. Arrange for urgent Hb/haematocrit.
- Leave on free drainage and attached to the drainage bag.
- Suture the pigtail to the skin securely, and cover with a sterile occlusive dressing.

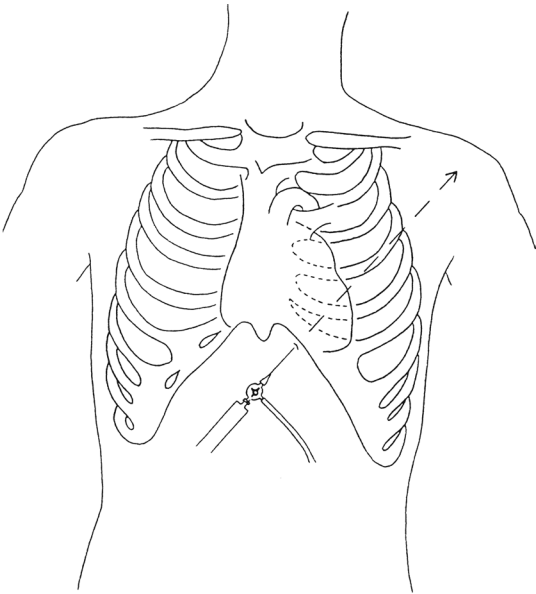


Fig. 15.9 Pericardial aspiration.

Pericardial aspiration 2

Aftercare

- Closely observe the patient for recurrent tamponade (obstruction of the drain), and repeat Echo.
- Discontinue anticoagulants.
- Remove the drain after 24h or when drainage stops.
- Consider the need for surgery (drainage, biopsy, or pericardial window) or specific therapy (chemotherapy if malignant effusion, antimicrobials if bacterial, dialysis if renal failure, etc.).

See Box 15.4 for complications of pericardiocentesis.

Tips and pitfalls

If the needle touches the heart's epicardial surface

You may feel a 'ticking' sensation transmitted down the needle—withdraw the needle a few millimetres; angulate the needle more superficially, and try cautiously again, aspirating as you advance.

If you do not enter the effusion

- Withdraw the needle slightly and advance again, aiming slightly deeper, but still towards the left shoulder.
- If this fails, try again, aiming more medially (mid-clavicular point or even suprasternal notch).
- Consider trying the apical approach (starting laterally at the cardiac apex and aiming for the right shoulder) if Echo confirms sufficient fluid at the cardiac apex.

Difficulty in inserting the pigtail

- This may be because of insufficient dilatation of the tract.
- Hold the wire tort (by gentle traction), while pushing the catheter; take care not to pull the wire out of the pericardium.

Haemorrhagic effusion versus blood

- Compare the Hb of the pericardial fluid to venous blood Hb.
- Place some of the fluid in a clean container; blood will clot, whereas a haemorrhagic effusion will not, as the 'whipping' action of the heart tends to defibrinate it.
- Confirm the position of the needle by first withdrawing some fluid and then injecting 10–20mL of contrast; using fluoroscopy, see if the contrast stays within the cardiac silhouette.
- Alternatively, if using Echo guidance, inject 5–10mL of saline into the needle, looking for 'microbubble contrast' in the cavity containing the needle tip. Injecting 20mL of saline rapidly into a peripheral vein will produce 'contrast' in the RA and RV and may allow them to be distinguished from the pericardial space.
- Connect a pressure line to the needle; a characteristic waveform will confirm penetration of the RV (see Fig. 15.6).

Box 15.4 Complications of pericardiocentesis

- Penetration of a cardiac chamber (usually RV).
- Laceration of an epicardial vessel.
- Arrhythmia (atrial arrhythmias as the wire is advanced, ventricular arrhythmias if the RV is penetrated).
- Pneumothorax.
- Perforation of the abdominal viscus (liver, stomach, colon).
- Ascending infection.

DC cardioversion 1

Relative contraindications

- Digoxin toxicity.
- Electrolyte disturbance ($\downarrow\text{Na}^+$, $\downarrow\text{K}^+$, $\downarrow\text{Ca}^{2+}$, $\downarrow\text{Mg}^{2+}$, acidosis).
- Inadequate anticoagulation and chronic AF.

See Box 15.5 for complications of DC cardioversion.

Checklist for DC cardioversion

- **Defibrillator:** Check this is functioning, with a fully equipped arrest trolley to hand in case of an arrest.
- **Informed consent:** (Unless life-threatening emergency.)
- **12-lead ECG:** AF, flutter, SVT, VT, signs of ischaemia or digoxin. If the ventricular rate is slow, have an external (transcutaneous) pacing system nearby in case of asystole.
- **NBM:** For at least 4h.
- **Anticoagulation:** Does the patient require anticoagulants? Is the INR >2.0 ? (Has it been so for >3 weeks?)
- **K^+ :** Check this is $>3.5\text{mmol/L}$.
- **Digoxin:** Check there are no features of digoxin toxicity and recent digoxin levels are normal. If there are frequent ventricular ectopics, give IV Mg^{2+} 8mmol.
- **Thyroid function:** Treat thyrotoxicosis or myxoedema first.
- **IV access:** Peripheral venous cannula.
- **Sedation:** Short general anaesthesia (propofol) is preferable to sedation with benzodiazepine and fentanyl. Bag the patient with 100% O_2 .
- **Select energy:** See Table 15.2.
- **Synchronization:** Check this is selected on the defibrillator for all shocks (unless the patient is in VF or haemodynamically unstable). Adjust the ECG gain, so that the machine is only sensing QRS complexes, and not P or T waves.
- **Paddle placement:** Most centres now use 'hands-free' adhesive paddles for DC cardioversion. Some continue with the traditional handheld paddles.
Conductive gel pads should be placed between the right of the sternum and the other to the left of the left nipple (anterior to mid-axillary line). Alternatively, place one anteriorly just left of the sternum, and one posteriorly to the left of the midline. There is some evidence that the anteroposterior (AP) position is superior for AF.
- **Cardioversion:** Check no one is in contact with the patient or with the metal bed. Ensure your own legs are clear of the bed! Apply firm pressure on the paddles if using the handheld device.
- **Unsuccessful:** Double the energy level, and repeat up to 360J. Consider changing the paddle position (see  'Paddle placement' earlier in the table). If prolonged sinus pause or ventricular arrhythmia during an elective procedure, stop.

- When complete, repeat ECG. Place in the recovery position until awake. Monitor for 2–4h, and ensure the effects of sedation have passed. Patients should be accompanied home by a friend or relative if being discharged.

Box 15.5 Complications of DC cardioversion

- Asystole/bradycardias.
- VF.
- Thromboembolism.
- Transient hypotension.
- Skin burns.
- Aspiration pneumonitis.

Table 15.2 Suggested initial energies for DC shock for elective cardioversion

Sustained VT	200J	Synchronized
AF	50–100J	Synchronized
Atrial flutter	50J	Synchronized
Other SVTs	50J	Synchronized

- If the initial shock is unsuccessful, increase the energy (50, 100, 200, 360J) and repeat.
- If still unsuccessful, consider changing the paddle position and try 360J again. It is inappropriate to persist further with elective DC cardioversion.

DC cardioversion 2

Notes

Anticoagulation

The risk of thromboembolism in patients with chronic AF and dilated cardiomyopathy is 0–7%, depending on the underlying risk factors.

Increased risk

- Prior embolic event.
- Mechanical heart valve.
- Mitral stenosis.
- Dilated LA.

Low risk

- Age <60 years.
- No heart disease.
- Recent-onset AF (<3 days).

Anticoagulate patients at risk with warfarin for at least 3–4 weeks. For recent-onset AF (1–3 days), anticoagulate with IV heparin for at least 12–24h and, if possible, exclude an intracardiac thrombus with TOE prior to DC shock. If there is a thrombus, anticoagulate with warfarin, as described earlier. For emergency cardioversion of AF (<24h), heparinize prior to shock.

The risk of systemic embolism with cardioversion of atrial flutter and other tachyarrhythmias is very low, provided there is no ventricular thrombus, since the coordinated atrial activity prevents the formation of a clot. Routine anticoagulation with warfarin is not necessary, but we would recommend heparin before DC shock, as the atria are often rendered mechanically stationary for several hours after shock, even though there is coordinate electrical depolarization.

After successful cardioversion, if the patient is on warfarin, continue anticoagulation for at least 3–4 weeks. Consider indefinite anticoagulation if there is intrinsic cardiac disease (e.g. mitral stenosis) or recurrent AF.

Special situations

Pregnancy

DC shock during pregnancy appears to be safe. Auscultate the fetal heart before and after cardioversion and, if possible, the fetal ECG should be monitored.

Pacemakers

There is a danger of damage to the pacemaker generator box or the junction at the tip of the pacing wire(s) and endocardium. Position the paddles in the AP position, as this is theoretically safer. Facilities for backup pacing (external or transvenous) should be available. Check the pacemaker post-cardioversion—both early and late problems have been reported.

Intra-aortic balloon counterpulsation 1

Indications

- Cardiogenic shock post-MI.
- Acute severe MR.
- Acute VSD.
- Preoperative (ostial left coronary stenosis).
- Weaning from cardiopulmonary bypass.

Rarely

- Treatment of ventricular arrhythmias post-MI.
- UA (as a bridge to CABG).

Contraindications

- AR.
- Dilated cardiomyopathy.
- Aortic dissection.
- Severe aorto-iliac atheroma.
- Bleeding diathesis.

Complications

- Aortic dissection.
- Thrombocytopenia.
- Arterial perforation
- Peripheral embolism.
- Limb ischaemia.
- Balloon rupture.

Principle

The device consists of a catheter with a balloon (40mL size) at its tip which is positioned in the descending thoracic aorta. Balloon inflation/deflation is synchronized to the ECG. The balloon should inflate just after the aortic notch (in diastole), thereby increasing pressure in the aortic root and increasing coronary perfusion. The balloon deflates just before ventricular systole, thereby decreasing afterload and improving LV performance (see Fig. 15.10).

Counterpulsation has many beneficial effects on the circulation:

- ↑ coronary perfusion in diastole.
- Reduced LVEDP.
- Reduced myocardial O₂ consumption.
- ↑ cerebral and peripheral blood flow.

The intra-aortic balloon cannot assist the patient in asystole or VF; it requires a minimum cardiac index of 1.2–1.4L/min/m², often necessitating additional inotropes.

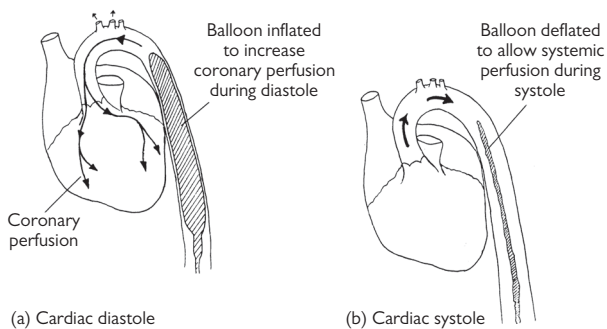


Fig. 15.10 Intra-aortic balloon counterpulsation.

Intra-aortic balloon counterpulsation 2

Technique

Balloon insertion

Previous experience is essential. Formerly, a cut-down to the femoral artery was required, but newer balloons come equipped with a sheath which may be introduced percutaneously. Using fluoroscopy, the balloon is positioned in the descending thoracic aorta, with the tip just below the origin of the left subclavian artery. Fully anticoagulate the patient with IV heparin. Some units routinely give IV antibiotics (flucloxacillin) to cover against *Staphylococcus* infection.

Triggering and timing

The balloon pump may be triggered either from the patient's ECG (R wave) or from the arterial pressure waveform. Slide switches on the pump allow precise timing of inflation and deflation during the cardiac cycle. Set the pump to 1:2 to allow you to see the effects of augmentation on alternate beats.

Troubleshooting

- Seek help from an expert! There is usually an on-call cardiac perfusionist or technician, a senior cardiac physician, or a surgeon.
- Counterpulsation is inefficient with HRs over 130bpm. Consider antiarrhythmics or 1:2 augmentation instead.
- Triggering and timing: for ECG triggering, select a lead with the most pronounced R wave; ensure that the pump is set to trigger from the ECG, not pressure; permanent pacemakers may interfere with triggering-select lead with negative and smallest pacing artefacts. Alternatively, set the pump to be triggered from the external pacing device. A good arterial waveform is required for pressure triggering; the timing will vary slightly, depending on the location of the arterial line (slightly earlier for radial artery line, cf. femoral artery line). Be guided by the haemodynamic effects of balloon inflation and deflation, rather than the precise value of delay.
- Limb ischaemia: exacerbated by poor cardiac output, adrenaline, NA, and peripheral vascular disease. Wean off and remove the balloon (see  IABP removal, p. 824).
- Thrombocytopenia: commonly seen; does not require transfusion, unless there is overt bleeding, and returns to normal once the balloon is removed. Consider epoprostenol infusion if platelet counts fall below $100 \times 10^9/L$.

IABP removal

- The patient may be progressively weaned by gradually reducing the counterpulsation ratio (1:2, 1:4, 1:8, etc.) and/or reducing the balloon volume and checking that the patient remains haemodynamically stable.
- Stop the heparin infusion, and wait for the ACT to fall <150s (APTT <1.5 normal).
- Using a 50mL syringe, have an assistant apply negative pressure to the balloon.
- Pull the balloon down until it abuts the sheath; do not attempt to pull the balloon into the sheath.
- Withdraw both balloon and sheath, and apply firm pressure on the femoral puncture site for at least 30min or until bleeding is controlled.

Principles of respiratory support

The aim of therapy is to relieve hypoxia and maintain or restore a normal PaCO_2 for the individual. Relative indications for mechanical ventilation are discussed in the appropriate chapters. This section discusses some of the principles involved.

Oxygen therapy

- O_2 should be administered by a system that delivers a defined percentage, between 28% and 100%, according to the patient's requirements (e.g. via fixed-percentage delivery masks such as Ventimask Mk IV).
- A Hudson mask or nasal cannulae give very variable FiO_2 , depending on the flow rate and the patient's breathing pattern.
- Nasal prongs only deliver at FiO_2 of 30% at flows of 2L/min, and become less efficient at higher flow rates (>35% at 3L/min, with little further increase with increasing flow). Higher flow rates require humidification.
- A properly positioned high-flow O_2 mask, using O_2 at 6L/min, can provide an FiO_2 of 60%.
- Combining nasal prongs and a high-flow mask can achieve an FiO_2 of >80–90%.
- In practice, it is rarely possible to consistently deliver >60%, unless using CPAP or ventilation.
- When sudden deterioration in oxygenation occurs, check the delivery system for empty cylinders, disconnected tubing, etc.

Indications

- Type 1 or 2 respiratory failure.
- Bronchial asthma.
- Acute MI.
- Sickle-cell crisis.
- CO poisoning.
- Cluster headaches.

Complications

- Tracheobronchitis occurs with prolonged inhalation of $\geq 80\% \text{ O}_2$. It causes retrosternal pain, cough, and dyspnoea.
- Parenchymal lung damage from O_2 occurs with $\text{FiO}_2 > 60\%$ for >48h without intermittent air breathing periods.

Monitoring oxygen therapy

- O_2 therapy should be assessed by continuous oximetry and intermittent ABGs.
- Oximetry is an invaluable aid but has limitations. In some situations (e.g. GBS), falling oximetry is a very late marker of impending respiratory failure, and CO_2 accumulation (e.g. in COPD) is clearly not monitored by oximetry. An SaO_2 of 93% correlates with a PaO_2 of 8kPa, and below 92%, the PaO_2 may fall disproportionately quickly.

Lung expansion techniques

- Periodic 'sighs' are a normal part of breathing and reverse microatelectasis. Lung expansion techniques are indicated for patients who cannot or will not take periodic large breaths (e.g. post-abdominal or chest surgery, neuromuscular chest wall weakness).
- Post-operative techniques used commonly by physiotherapists include incentive spirometry, coached maximal inspiration with cough, postural drainage, and chest percussion.
- Volume-generating devices, such as '*the Bird*', are triggered by the patient initiating inspiration and deliver a preset tidal volume to augment the patient's breath. Liaise with your physiotherapist.
- Pressure-generating techniques [such as CPAP, nasal intermittent positive pressure ventilation (NIPPV), and bilevel positive airway pressure (BiPAP)] have the advantage that, even if a leak develops around the mask, the ventilator is able to 'compensate' to provide the prescribed positive pressure (see following sections).
- For both volume- and pressure-generating techniques, the patient must be able to protect their airway and generate enough effort to trigger the machine.

Continuous positive airways pressure

- CPAP provides a constant positive pressure throughout the respiratory cycle.
- It acts to splint open collapsing alveoli which may be full of fluid (or a collapsing upper airway in OSA), increases functional residual capacity (FRC) and compliance, such that the work of breathing is reduced and gas exchange is improved.
- It allows a higher FiO_2 (approaching 80–100%) to be administered, cf. standard O_2 delivery masks.
- CPAP should usually be commenced after liaison with anaesthetists; in a patient for active management, it should usually be started on the ITU.
- A standard starting pressure is $5\text{cmH}_2\text{O}$.

Indications

- Pulmonary oedema.
- Acute respiratory failure (e.g. secondary to infection) where a simple face mask for O_2 is insufficient.
- Acute respiratory failure where ventilation is inappropriate.
- Weaning from the ventilator.
- OSA.
- Patient needs to:
 - Be awake and alert.
 - Be able to protect the airway.
 - Possess adequate respiratory muscle strength.
 - Be haemodynamically stable.

Mechanical ventilation

Negative pressure ventilation (NPV)

- This works by 'sucking' out the chest wall and is used in chronic hypoventilation (e.g. polio, kyphoscoliosis, or muscle disease). Expiration is passive.
- These techniques do not require tracheal intubation. However, access to the patient for nursing care is difficult.

Intermittent positive pressure ventilation (IPPV)

Indications

Deteriorating gas exchange due to a potentially reversible cause of respiratory failure:

- Pneumonia.
- Head injury.
- Exacerbation of COPD.
- Cerebral hypoxia.
- Massive atelectasis (e.g. post-cardiac arrest).
- Respiratory muscle weakness.
- Intracranial bleed.
- Myasthenia gravis.
- Raised ICP.
- Acute infective polyneuritis.
- Major trauma or burns.

Ventilation of the ill patient on the ITU is via either an ETT or a tracheostomy. If ventilation is anticipated to be needed for >1 week, consider a tracheostomy.

There are two basic types of ventilator.

- *Pressure-cycled ventilators* deliver gas into the lungs until a prescribed pressure is reached, when inspiratory flow stops and, after a short pause, expiration occurs by passive recoil. This has the advantage of reducing the peak airway pressures without impairing cardiac performance in situations such as ARDS. However, if the airway pressures increase or compliance decreases, the tidal volume will fall, so patients need to be monitored closely to avoid hypoventilation.
- *Volume-cycled ventilators* deliver a preset tidal volume into the lungs over a predetermined inspiratory time (usually ~30% of the breathing cycle), hold the breath in the lungs (for ~10% of the cycle), and then allow passive expiration as the lungs recoil.

Nasal ventilation

- NIPPV delivers positive pressure for a prescribed inspiratory time, when triggered by the patient initiating a breath, allowing the patient to exhale to atmospheric pressure.
- The positive pressure is supplied by a small machine via a tight-fitting nasal mask.
- It is generally used as a method of home nocturnal ventilation for patients with severe musculoskeletal chest wall disease (e.g. kyphoscoliosis) or with OSA.
- It has also been used, with modest success, as an alternative to formal ventilation via ETT in patients where positive *expiratory* pressure is not desirable, e.g. acute asthma, COPD with CO₂ retention, and as a weaning aid in those in whom separation from a ventilator is proving difficult.
- The system is relatively easy to set up by experienced personnel, but some patients take to it better than others. It should not be commenced by inexperienced personnel.

Positive pressure ventilation

Continuous mandatory ventilation

- Continuous mandatory ventilation (CMV) acts on a preset cycle to deliver a given number of breaths per minute of a set volume. The duration of the cycle determines the breath frequency.
- The *minute volume* is calculated by (tidal volume $\times$ frequency).
- The relative proportions of time spent in inspiration and expiration (I:E ratio) is normally set at 1:2 but may be altered. For example, in acute asthma, where air trapping is a problem, a longer expiratory time is needed (➡ Acute severe asthma: further management, p. 188); in ARDS, where the lung compliance is low, a longer inspiratory time is beneficial (inverse ratio ventilation; ➡ Adult respiratory distress syndrome 2, p. 206).
- The patients should be fully sedated. Patients capable of spontaneous breaths who are ventilated on CMV can get 'stacking' of breaths where the ventilator working on its preset cycle may give a breath on top of one which the patient has just taken, leading to overinflation of the lungs, a high peak inspiratory pressure, and the risk of pneumothorax.
- Prolonged use of this mode will result in atrophy of the respiratory muscles; this may prove difficult in subsequent 'weaning', especially in combination with proximal myopathy from steroids, e.g. in acute asthma.
- Ventilation may either be terminated abruptly or by gradual transfer of the ventilatory workload from the machine to the patient ('weaning').

Synchronized intermittent mandatory ventilation

- Synchronized intermittent mandatory ventilation (SIMV) modes allow the patient to breath spontaneously and be effectively ventilated, and allows gradual transfer of the work of breathing on to the patient. This may be appropriate when weaning the patient whose respiratory muscles have wasted. It is inappropriate in acutely ill patients (e.g. acute severe asthma, ARDS); CMV with sedation reduces O_2 requirement and respiratory drive, and allows more effective ventilation.
- Exact details of the methods of synchronization vary between machines, but all act in a similar manner—the patient breathes spontaneously through the ventilator circuit. The ventilator is usually preset to ensure that the patient has a minimum number of breaths per minute, and if the number of spontaneous breaths falls below the preset level, then a breath is delivered by the machine.
- Most SIMV modes of ventilation provide some form of positive pressure support to the patient's spontaneous breaths, to reduce the work of breathing and ensure effective ventilation (see ➡ Pressure support, p. 831).

Pressure support

- Positive pressure is added during inspiration to relieve part or all of the work of breathing.
- This may be done in conjunction with an SIMV mode of ventilation or as a means of supporting entirely spontaneous patient-triggered ventilation during the process of weaning.
- It allows the patients to determine their own RR and should ensure adequate inflation of the lungs and oxygenation. It is, however, only suitable for those whose lung function is reasonably adequate and who are not confused or exhausted.

Positive end-expiratory pressure

- PEEP is a preset pressure added to the end of expiration only, to maintain the lung volume, prevent airway or alveolar collapse, and open up atelectatic or fluid-filled lungs (e.g. in ARDS or cardiogenic pulmonary oedema).
- It can significantly improve oxygenation by making more of the lung available for gas exchange. However, the trade-off is an increase in intrathoracic pressure, which can significantly decrease venous return and hence cardiac output. There is also an ↑ risk of pneumothorax.
- 'Auto-PEEP' is seen if the patient's lungs do not fully empty before the next inflation (e.g. asthma).
- In general, PEEP should be kept at a level of 5–10cmH₂O, where required, and the level adjusted in 2–3cmH₂O intervals every 20–30min, according to a balance between oxygenation and cardiac performance.
- Measurement and interpretation of PCWP in patients on PEEP depend on the position of the catheter. PCWP will always reflect pulmonary venous pressures if they are greater than PEEP. If the catheter is in an apical vessel where the PCWP is normally lower, due to the effects of gravity, the pressure measured may be the alveolar (PEEP) pressure, rather than the true PCWP; in a dependent area, the pressures are more accurate. Removing PEEP during measurement alters the haemodynamics and oxygenation, and the pressures do not reflect the state once back on the ventilator.

Percutaneous cricothyrotomy

Indications

- To bypass upper airway obstruction (e.g. trauma, infections, neoplasms, post-operative, burns, and corrosives) when oral or nasotracheal intubation is contraindicated.
- In situations when ET intubations fail (e.g. massive nasopharyngeal haemorrhage, structural deformities, obstruction due to foreign bodies, etc.).

Percutaneous cricothyrotomy

The Seldinger technique is quicker, may be performed by non-surgeons at the bedside, and is safer (see Fig. 15.11). After anaesthetizing the area, a needle is used to puncture the cricothyroid membrane, and, through this, a guidewire is introduced into the trachea. Over this, a series of dilators and a tracheostomy tube can be safely positioned.

Complications of cricothyrotomy

- Haemorrhage.
- Subglottic stenosis.
- Hoarseness.
- Laryngotracheal-cutaneous fistula.

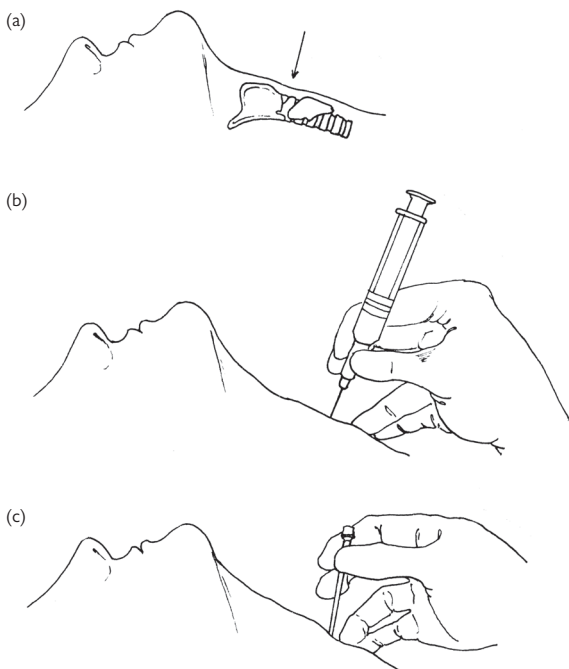


Fig. 15.11 Needle cricothyroidotomy.

Endotracheal intubation

This is the best method for providing and maintaining a clear airway for ventilation, protection against aspiration, and suctioning and clearing lower respiratory tract secretions. The most common indication for urgent intubation by a physician is cardiac arrest. This is not a technique for the inexperienced—the description given here is not intended as a substitute for practice under supervision of a skilled anaesthetist.

You will need

- Laryngoscope, usually with a curved blade (Macintosh).
- ETT (8–9mm internal diameter for ♂ and 7–8mm for ♀) and appropriate adaptors.
- Syringe for cuff inflation, and clamp to prevent air escaping from the cuff once inflated.
- Scissors and tape or bandage to secure the tube.
- Lubricating jelly (e.g. K-Y® jelly).
- Suction apparatus with rigid (Yankauer) and long, flexible catheters.

Potential problems during intubation

- Certain anatomical variations (e.g. receding mandible, short neck, prominent incisors, high-arched palate), as well as stiff neck or trismus, may make intubation complicated; summon experienced help.
- Vomiting: suction if necessary. Cricoid pressure may be useful.
- Cervical spine injury: immobilize the head and neck in line with the body, and try not to extend the head during intubation.
- Facial burns or trauma may make orotracheal intubation impossible. Consider cricothyrotomy (➡ Percutaneous cricothyrotomy, p. 832).

Procedure

(See Fig. 15.12.)

- Place the patient with the neck slightly flexed and the head extended. Take care if cervical injury is suspected.
- Cricoid pressure: the oesophagus can be occluded by compressing the cricoid cartilage posteriorly against the body of C6. This prevents passive regurgitation into the trachea, but not active vomiting. Ask your assistant to maintain pressure until the tube is in place and the cuff inflated.
- Pre-oxygenate the patient by hyperventilation with $\geq 85\% \text{O}_2$ for 15–30s. Suction the throat to clear the airway.
- With the laryngoscope in your left hand, insert the blade on the right side of the mouth. Advance to the base of the tongue, identifying the tonsillar fossa and the uvula. Push the blade to the left, moving the tongue over. Advance the blade until the epiglottis comes into view.
- Insert the blade tip between the base of the tongue and the epiglottis, and pull the whole blade (and larynx) upwards along the line of the handle of the laryngoscope to expose the vocal cords. Brief suction may be necessary to clear the view.
- Insert the ETT between the vocal cords, and advance it until the cuff is just below the cords and no further. Inflate the cuff with air.

- If the cords cannot be seen, do not poke at the epiglottis, hoping for success; call for more skilled help, and revert to basic airway management.
- Intubation must not take longer than 30s; if there is any doubt about the position, remove the tube, reoxygenate, and try again.
- With the tube in place, listen to the chest during inflation to check that *both* sides of the chest inflate. If the tube is in the oesophagus, chest expansion will be minimal, though the stomach may inflate.
- Tie the ETT in place to prevent it from slipping up or down the airway. Ventilate with high-concentration O₂.

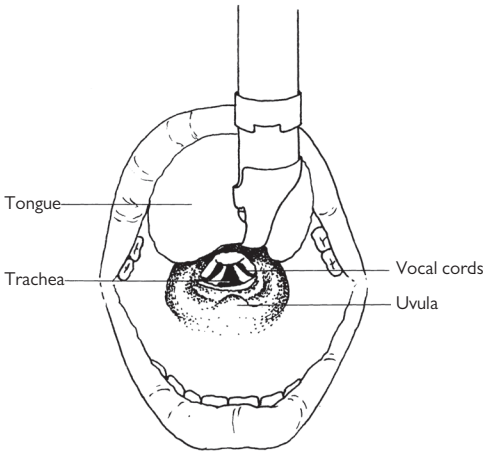


Fig. 15.12 Landmarks for endotracheal intubation.

Aspiration of pneumothorax

If the pneumothorax is $<75\%$ and the patient is haemodynamically stable, it is reasonable to attempt aspiration of the pneumothorax in the first instance (➡ Pneumothorax: assessment, pp. 210–11).

You will need

- 10mL and 50mL syringes with green (18G) and orange (25G) needles.
- Dressing pack (swabs, sterile drapes, antiseptic) and sterile gloves.
- 19G Venflon® or alternative cannula.
- Local anaesthetic (e.g. 2% lidocaine).
- A 3-way tap.

Procedure

- One assistant is required.
- Sit the patient up, propped against pillows, with their hand behind their head; ensure you are comfortable and on a similar level.
- Select the space to aspirate—the second intercostal space in the mid-clavicular line. Confirm with a CXR that you are aspirating the correct side (a surprisingly common cause of disasters is aspirating the normal side).
- Clean the skin and use an aseptic technique.
- Connect a 50mL syringe to a 3-way tap in readiness, with the line which will be connected to the patient turned 'off' so that no air will enter the pleural cavity on connecting the apparatus.
- Infiltrate 5–10mL of lidocaine from the skin to pleura, just above the upper border of the rib in the space you are using. Confirm the presence of air by aspirating ~5mL via a green needle.
- Insert a 16G or larger IV cannula into the pneumothorax, preferably while aspirating the cannula with a syringe, so that entry into the pleural space is confirmed. Allow the tip of the cannula to enter the space by ~1cm.
- Ask the patient to hold their breath, and remove the needle. Swiftly connect the 3-way tap. Aspirate 50mL of air/fluid, and void it through the other lumen of the tap. Repeat.
- Aspiration should be stopped when resistance to suction is felt, the patient coughs excessively, or $\geq 2.5\text{L}$ of air has been aspirated.
- Withdraw the cannula, and cover the site with a dressing plaster (e.g. Elastoplast™ or Band-Aid™).
- Check a post-procedure CXR. If there is significant residual pneumothorax, insert a chest drain.

Aspiration of a pleural effusion

The basic procedure is similar to that for a pneumothorax; the site is different—one or two intercostal spaces posteriorly below the level at which dullness is detected. Ideally, all cases should have an USS first to confirm the level of the effusion and ensure that the diaphragm is not higher than anticipated due to underlying pulmonary collapse.

- Position the patient leaning forward over the back of a chair or table. Clean the skin, and infiltrate with local anaesthetic, as described for a pneumothorax aspiration.
- Insert the cannula, and aspirate the effusion with a 50mL syringe, voiding it through the 3-way tap. Repeat until resistance is felt and the tap is dry.
- Check a post-procedure CXR.

Insertion of a chest drain 1

You will need

- Dressing pack (sterile gauze, gloves, drapes, povidone-iodine).
- Local anaesthetic (720mL of 1% lidocaine), 10mL syringe, green (18G) and orange (25G) needles.
- Scalpel and No. 11 blade for skin incision; two packs of silk sutures (1–0).
- Two forceps (Kelly clamps), scissors, needle-holder (often prepackaged as a 'chest drain set').
- Where possible, use the new Seldinger-type chest tubes—especially for pneumothorax.
- Chest tubes—a selection of 24, 28, 32, and 36F.
- Chest drainage bottles, with sterile water for underwater seal.
- One assistant.

Procedure

- Position the patient leaning forward over the back of a chair or table. If possible, premedicate the patient with an appropriate amount of opiate ~30min before.
- Mark the space to be drained in the mid-axillary line—usually the fifth intercostal space for a pneumothorax, and below the level of the fluid for an effusion. Clean the skin.
- Select the chest tube: small (24F) for air alone, medium (28F) for serous fluid, or large (32–36F) for blood/pus. Remove the trocar. Check that the underwater seal bottles are ready.
- Infiltrate the skin with 15–20mL of lidocaine 1%. Make a short subcutaneous tunnel for the chest tube before it enters the pleural space (see Fig. 15.13). Anaesthetize the periosteum on the top of the rib. Check that you can aspirate air/fluid from the pleural space.
- Make a horizontal 2cm incision in the anaesthetized skin of the rib space. Use the forceps to blunt-dissect through the fat and intercostal muscles to make a track large enough for your gloved finger down to the pleural space. Stay close to the upper border of the rib to avoid the neurovascular bundle.
- Check the length of the tube against the patient's chest to confirm how much needs to be inserted into the patient's chest. Aim to get the tip to the apex for a pneumothorax; keep the lowermost hole as low as possible (>2cm into the chest) to drain pleural fluid.
- Insert two sutures across the incision (or a purse-string, see Fig. 15.13). These will gently tighten around the tube, once inserted, to create an airtight seal, but do not knot—these sutures will be used to close the wound after drain removal.
- Remove the trocar. Clamp the end of the tube with the forceps, and gently introduce the tube into the pleural space. Rotating the forceps 180° directs the tube to the apex (see Fig. 15.13). Condensation in the tube (or fluid) confirms the tube is within the pleural space. Check that all the holes are within the thorax and connect to the underwater seal. Tape these to the skin.

- Gently tighten the skin sutures, but do not knot. The drain should be secured with several other stitches and copious amounts of adhesive tape. They are very vulnerable to accidental traction.
- Wrap adhesive tape around the join between the drain and the connecting tubing.
- Prescribe adequate analgesia for the patient for when the local anaesthetic wears off.
- Arrange for a CXR to check the position of the drain.
- Do not drain off >1L of pleural fluid/24h to avoid re-expansion pulmonary oedema.

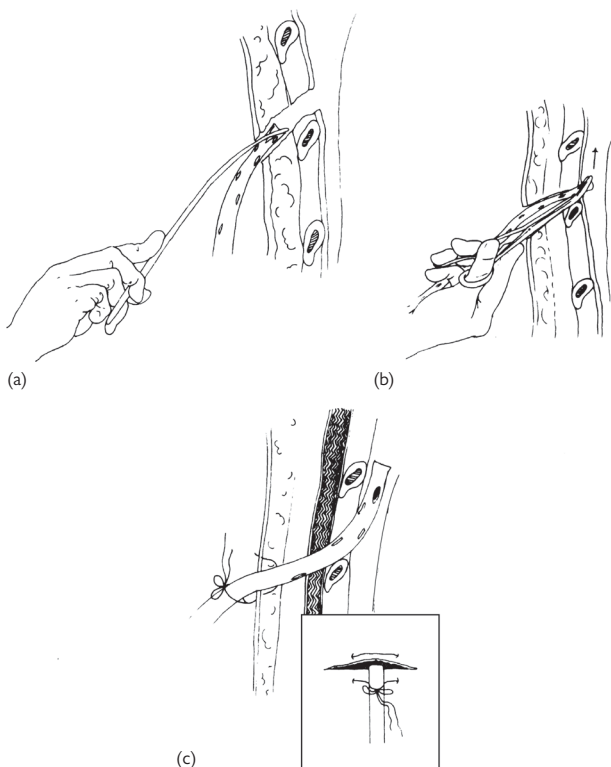


Fig. 15.13 Insertion of a chest drain.

Insertion of a chest drain 2

Tips and pitfalls

- The chest drain should only be left in place, while air or fluid continues to drain. The risk of an ascending infection increases with time. Prophylactic antibiotics are not usually indicated.

Malpositioned tube

- Obtain a CXR (and then daily) to check the position of the drain and examine the lung fields.
- If the drain is too far out, there will be an air leak and the patient may develop subcutaneous emphysema. Ideally, remove the drain and replace with a new drain at a new site; the risk of an ascending infection is high if the 'non-sterile' portion of the tube is just pushed into the chest.
- If the drain is too far in, it may be uncomfortable for the patient and impinge on vital structures (e.g. thoracic aorta). Pull the tube out the appropriate distance and re-suture.

Obstructed tube

- Check the water column in the chest drain bottle swings with respiration. This stops if the tube is obstructed.
- Check the drains and tubing are free of bends and kinks.
- Blood clots or fibrin may block the tube.
- If the lung is still collapsed on the CXR, replace the chest drain with a new tube at a new site.

Lung fails to re-expand

- This is either due to an obstructed system or a persistent air leak (e.g. tracheobronchial fistula).
- If the chest drain continues to bubble, apply suction to the drain to help expand the lung. Consider inserting further drains or surgical repair of the leak. If the chest drain is obstructed (described earlier), replace the drain.

Removing the chest drain

- *Do not* clamp the chest drain.
- Remove the dressings, and release the sutures holding the drain in place. Leave the skin incision sutures (purse-string) in position to close the wound once the drain is removed.
- Remove the drain in a gentle motion, either in inspiration or in expiration with Valsalva.
- Tighten the skin sutures. These should be removed after 3–4 days and a fresh dressing applied.
- Any residual pneumothorax should be treated, depending on the patient's symptoms.

Complications

- Bleeding (intercostal vessels; laceration of the lung, spleen, or liver).
- Pulmonary oedema (too rapid lung expansion).
- Empyema.
- Subcutaneous emphysema.
- Residual pneumothorax or effusion (malpositioned or obstructed chest drain).

Ascitic tap

Indications

- To diagnose or exclude SBP.
- To obtain ascites for measurement of protein, albumin, or amylase (pancreatic ascites).
- Ascitic cytology may require 100mL of fluid.
- Stain and culture for AFBs; lymphocytes: >500 cells/mm³).
- To drain cirrhotic or malignant ascites.

Relative contraindications

- Previous abdominal surgery increases the risk of perforation (due to adhesion of underlying bowel to the abdominal wall).
- Massive hepatomegaly or splenomegaly (avoid the same side).
- Massive ileus with bowel distension.

NB There are no clinical data to support avoiding paracentesis in severe coagulopathy (platelets $<20\,000$, INR >4.0), but most clinicians should be cautious and consider correcting coagulopathy.

Procedure

- Lie the patient supine and tilted slightly to one side.
- Select the site for paracentesis (e.g. on a horizontal line across the umbilicus, and 4cm lateral to a line passing to the mid-inguinal point). Clean the area with chlorhexidine. Avoid surgical scars (see Fig. 15.14).
- Use a 20mL syringe with a 18G (green) needle. In obese patients, use a longer needle (e.g. 18G Abbocath®). Infiltrate the area with local anaesthetic. Insert the needle slowly into the abdomen, while aspirating until fluid is obtained.
- Inoculate 5mL of the fluid into each bottle of a set of blood culture bottles, and send 5mL in a sterile bottle for microscopy and protein determination. Add 2mL of ascites to an EDTA tube (contains anticoagulant), and send to haematology for cell count.
- Remove and apply a sterile plaster over the puncture site.

Total paracentesis

Daily small-volume paracentesis increases the risk of complications such as infection and ascitic leakage. The risk of infection is high if a peritoneal drain is left *in situ* in cirrhotic ascites. It is safer to drain the ascites to dryness.

The rate of fluid drainage can be fast, and it is generally safe to drain >3–5L/h. During the first 3–6h of paracentesis, there is a significant increase in cardiac output, a decrease in SVR, and a modest fall in MAP (by 5–10mmHg). Tense ascites increases the RA pressure, which falls acutely following paracentesis.

Indications

- Tense or gross ascites.

Mortality

The paracentesis-related mortality rate is ~0.02% (1 in 5000).

Relative contraindications

- Previous abdominal surgery and scarring. Be cautious—avoid scars, and use USS guidance.
- Patients with clinically apparent DIC or fibrinolysis and oozing from needle-sticks.
- Paracentesis should not be performed in patients with a massive ileus with bowel distension without imaging guidance.
- Platelet count <20. Ignore the INR (FFP not required).
- Renal failure: the risk of bleeding is ↑ in renal failure, although this is NOT a contraindication, and diagnosis of infected ascites is important in this group of patients.
- It is important to avoid puncturing the superficial inferior epigastric artery, which runs just lateral to the umbilicus from the mid-inguinal point (see Fig. 15.14). Avoid any visible superficial veins.
- For USS-guided paracentesis, mark the spot prior to the procedure.
- The skin should be cleaned and sterilized. Use chlorhexidine pads. Anaesthetize the area (see 'X' in Fig. 15.14) with a small volume of lidocaine.
- Do NOT go too lateral, and the patient should be supine and leaning slightly to one side.
- Beware of patients with a very large spleen or very large liver, and avoid going too close to either structure. Use USS guidance, if possible.
- To avoid the catheter blocking due to omentum plugging the end, use a catheter with side-holes.

Insertion of drainage catheter and draining the ascites

- You will need to gown up with a sterile gown.
- Monitor the BP before, and hourly for the first 6h.
- Insert the drainage catheter with multiple side-holes provided (attached to a 20mL syringe), aspirating as one advances the cannula. When ascitic fluid is obtained, advance the needle 3–4cm more, and then advance the plastic cannula into the abdomen and attach the drainage system.
- Secure into place with adhesive tape, and leave on free drainage.

- Ask the patient to lie to one side, so that the drainage side is downmost (left or right).
- Allow all ascites to drain as quickly as it will come, regardless of the volume. When the ascites stops draining or slows down, move the patient from side to side and lie towards the drainage site.
- When complete, remove the catheter; apply plaster, and lie the patient with the *drainage site uppermost* for at least 4h (~100mL of 20% albumin for every 2.5L removed).
- Replace albumin with an infusion of 20% albumin to give 8g of albumin for every litre of ascites removed. It is usually best to start the albumin infusion after paracentesis is complete, but if there is a significant drop in BP, it can be started earlier.
- Try and ensure that all fluid is drained, as incomplete paracentesis increases the risk of leakage post-procedure.
- Measure the volume of ascites drained.
- Always remove the drainage catheter within 6h of insertion to decrease the risk of sepsis.

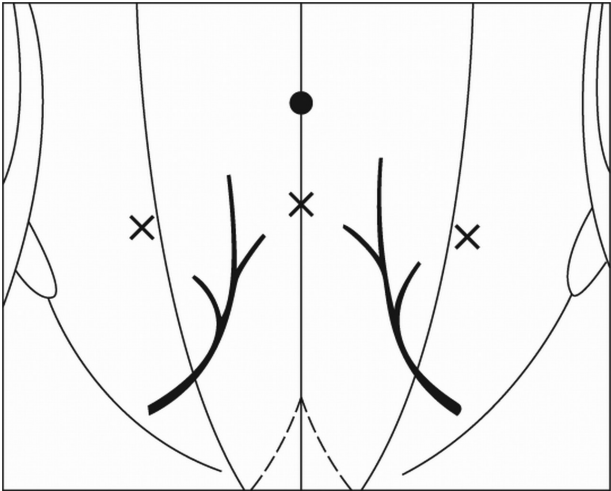


Fig. 15.14 Abdominal paracentesis sites. Reproduced from Watson, et al. *Oxford Handbook of Palliative Care* (2009), with permission from Oxford University Press.

Insertion of Sengstaken–Blakemore tube

The Sengstaken–Blakemore tube is inserted to control variceal bleeding when endoscopic therapy or IV terlipressin have failed. It should not be used as primary therapy, since it is unpleasant and increases the risk of oesophageal ulceration and aspiration.

Seek experienced or specialist help early. Balloon tamponade is a temporary procedure to prevent exsanguination.

Procedure

- It is assumed that the patient is undergoing resuscitation and has received IV terlipressin. To reduce the risk of aspiration, the patient should be intubated and ventilated.
- The Sengstaken tube should be stored in the fridge (to maximize stiffness) and removed just before use. Familiarize yourself with the ports before insertion. Check the integrity of the balloons before you insert the tube.
- Place an endoscope protection mouthguard in place (to prevent biting of the tube). Cover the end of the tube with lubricating jelly, and, with the patient in the left semi-prone position, push the tube down, asking the patient to swallow (if conscious). If the tube curls up in the mouth, try again.
- Estimate the length of the tube to be inserted by measuring from the bridge of the nose to the earlobe and adding the distance from the nose to the xiphoid process. This should equate to at least 50–60cm; make sure that the tube is not coiled up in the back of the mouth.
- Inflate the gastric balloon with 250mL of water. Clamp the balloon channel. Then gently pull back on the tube until the gastric balloon abuts the gastro-oesophageal junction (resistance felt), and then pull further until the patient is beginning to be tugged by pulling. Note the position at the edge of the mouthpiece (mark with a pen), and attach with a sticking plaster to the side of the face.
- *Tip:* if the above fails, place the tube through the mouthguard to the back of the throat, and then follow with an endoscope. The endoscope will push the tube down the oesophagus and can be retroverted to directly visualize the gastric balloon being filled, before being removed.
- In general, the oesophageal balloon should *never* be used. Virtually all bleeding varices occur at the oesophagogastric junction and are controlled using the gastric balloon.
- Do *not* leave the balloon inflated for >12h, since this increases the risk of oesophageal ulceration.
- Obtain a CXR to check the position of the tube.
- The gastric channel should be aspirated continuously.

Percutaneous liver biopsy

This should only be done by experienced doctors.

Procedure

Patients should be warned of the risk of bleeding, pneumothorax, gall bladder puncture, failed biopsy, and shoulder tip pain, which may last several hours. The mortality is ~1:10 000.

Relative contraindications

- PT >3s prolonged.
- Platelet count $<80 \times 10^9/L$ or bleeding diathesis.
- Ascites.
- Liver cancer (risk of tumour seeding).

Premedicate the patient with analgesia (e.g. 30–60mg of dihydrocodeine) before the procedure. The patient lies supine, with their right hand behind their head. Always carry out the liver biopsy under US guidance, especially if the liver is small and cirrhotic. The skin is cleaned, local anaesthetic infiltrated down to the liver capsule, and a liver biopsy needle is inserted when the breath is held in expiration. The biopsy itself takes about 5–10s and may cause shoulder tip pain.

A plugged biopsy can be performed when the PT is up to 6s prolonged, with a platelet count of $>40\,000\text{mm}^3$. The biopsy is done through a sheath, and the tract embolized using Gelfoam® to prevent bleeding.

Transjugular liver biopsy

This liver biopsy is taken through the hepatic vein, with secondary bleeding occurring into the circulation. It is not without risk, as the hepatic capsule may be punctured, leading to bleeding. It is used for patients in whom a prolonged PT or low platelet count precludes a normal liver biopsy.

A large introducer is placed into the IJV. A catheter is introduced through this and manipulated into the hepatic vein. The catheter is removed, leaving a guidewire *in situ*. A metal transjugular biopsy needle is passed over the wire and advanced into the hepatic vein. One has to avoid being too peripheral (risk of capsular puncture). The wire is removed, and the needle advanced while suction is applied. A biopsy is obtained by the ‘Menghini’ technique. The biopsies obtained are smaller and more fragmented than those obtained by conventional techniques.

Transjugular intrahepatic portosystemic shunt

Indications

- Uncontrolled bleeding of oesophageal or gastric varices.
- Diuretic-resistant ascites.
- Hepatic hydrothorax.

Principle

To decrease the portal pressure acutely, a shunt is placed between the hepatic vein and a portal vein tributary. Blood then flows from the high-pressure portal system to the lower-pressure hepatic venous system which drains into the IVC.

It is carried out in specialist centres and is technically quite difficult. It does not require a general anaesthetic, and it does not hinder future liver transplantation.

Method

The IJV is catheterized, and a cannula passed through the RA into the IVC and into the hepatic vein. The portal vein is localized by USS, and a metal transjugular biopsy needle pushed through the liver from the hepatic vein into a portal vein tributary (usually the right portal vein). A wire is then passed into the portal vein and the metal needle withdrawn, leaving the wire joining the hepatic vein and portal vein. An expandable stent is then passed over the wire. A typical stent size is 8–12mm.

Complications

- Immediate mortality is 2–3%, usually from a capsular puncture and bleeding. The 4- to 6-week mortality in patients treated by TIPS for uncontrolled haemorrhage is up to 50% (from cirrhosis).
- Hepatic encephalopathy occurs in 20%.
- Failure to reduce portal pressure may occur if there are large extrahepatic shunts. These may need to be embolized.

Peritoneal dialysis

Rarely used but does not require vascular access or anticoagulation. A clearance rate of ~10mL/min may be achieved.

It requires:

- A peritoneal dialysis (PD) catheter (inserted under local anaesthesia).
- An intact peritoneal cavity free of infection, herniae, and adhesions.

Complications

Peritonitis occurs at 0.8 episode per patient per year.

Assessment

- Features of peritonitis are: cloudy PD bag (99%), abdominal pain (95%), and abdominal tenderness (80%).
- Other features include: fever (33%), nausea and vomiting (30%), leucocytosis (25%), and diarrhoea or constipation (15%).
- Investigations: PD effluent cell count (peritonitis if >100 neutrophils/ mm^3); culture PD fluid (inoculate a blood culture bottle); Gram-stain PD fluid; FBC (for leucocytosis); blood cultures.

Management

- All patients require antibiotics but may not require admission. The antibiotics used depend on Gram stain and culture results. A typical protocol would be ciprofloxacin or vancomycin, plus metronidazole. Patients with high fever with leucocytosis and/or who are systemically unwell warrant IV antibiotics.
- Gram -ve infection, in particular *Pseudomonas*, is associated with more severe infection.
- Peritonitis can lead to the development of an ileus.
- Patients may lose up to 25g of protein/day in severe cases and should receive adequate nutritional support.
- If the infection is resistant to treatment, consider removal of the Tenckhoff catheter and atypical organisms (e.g. fungi).
- Consider an underlying GI pathology, especially if multibacterial, Gram -ve organisms, or other symptoms.

Other problems

Mild cases of fluid overload may respond to hypertonic exchanges (6.36% or 4.25% glucose), fluid restriction (1L/day), and large doses of diuretics (e.g. furosemide 500mg bd).

Other problems include poor exchanges, malposition of the catheter, omental blocking, fibrin deposition, and hyperglycaemia.

Intermittent haemodialysis

A blood flow of 250–300mL/min is needed across the dialysis membrane and leads to a clearance of 20mL/min.

- *Vascular access*: vascular access may be obtained using an arteriovenous shunt involving the radial artery or, more commonly, by using a Vascath which uses venous, rather than arterial, blood.
- *Anticoagulation*: heparin is normally used. If contraindicated, e.g. recent haemorrhage, then epoprostenol may be used but may cause hypotension and abdominal cramps.
- *Haemodynamic stability*: patients with MOF commonly develop hypotension during haemodialysis. This may be ameliorated by high-sodium dialysate and priming the circuit with 4.5% human albumin solution.

Complications of haemodialysis

Hypotension

Usually occurs within the first 15min of commencing dialysis. It probably involves activation of circulating inflammatory cells by the membrane, osmotic shifts, and possibly loss of fluid. *Treatment*: cautious fluid replacement and inotropes (watch for pulmonary oedema if overtransfused).

Dialysis disequilibrium

This occurs during the initial dialysis, especially in patients with marked uraemia, and is more common in patients with pre-existing neurological disease. *Clinical features*: headache, nausea and vomiting, fits, cerebral oedema. *Treatment*: treat cerebral oedema as described under ➔ Intracerebral haemorrhage, pp. 398–9. Short and slow initial dialyses may prevent this.

Dialyser reaction

This is caused by an IgE or complement response against the ethylene oxide component (sterilizing agent) or the cellulose component. Use of 'biocompatible' membranes, e.g. polysulfone, polyacrylonitrile (PAN), or dialysers sterilized by steam or gamma-irradiation may prevent further reactions.

Haemofiltration

Continuous arteriovenous haemofiltration (CAVH) implies bulk solute transport across a membrane and replacement. Continuous arteriovenous haemodiafiltration (CAVHD) involves pumping of dialysate across the other side of the membrane. For both, arterial blood (driven by arterial pressure) is continuously filtered at a relatively low flow rate (50–100mL/min). Continuous venovenous haemofiltration (CVVH) and continuous venovenous haemodiafiltration (CVVHD) involve pumping blood from a venous access to the dialysis membrane (150–200mL/min). The equivalent GFR obtained by these are 15–30mL/min. These are used most commonly on ITU. Both of these methods cause less haemodynamic instability and are particularly useful in patients with MOF.

Plasmapheresis

A therapy directed towards removal of circulating high-molecular-weight compounds not removed by dialysis. Particularly used in the removal of antibodies or lipoproteins.

Indications

- Myasthenia gravis.
- GBS.
- Goodpasture's syndrome.
- TTP.
- HUS.
- Severe hyperlipidaemia
- Multisystem vasculitis.
- Hyperviscosity syndrome (e.g. Waldenström's macroglobulinaemia).
- HLA antibody removal.

Method

Requires central venous access with a large-bore, dual-lumen cannula. Usually five treatment sessions are given on consecutive days. Plasma is removed and replaced with typically 2U of FFP and 3L of 4.5% albumin. IV Ca^{2+} (10mL of 10% calcium gluconate) should be given with the FFP. Febrile reactions may occur, as with other blood products. Plasmapheresis has no effect on the underlying rate of antibody production but is a useful treatment in acute situations such as Goodpasture's syndrome and myasthenia gravis.

- For HUS and TTP, one must use FFP *only* (preferably cryodepleted), usually a minimum of 3L/day (➡ Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, p. 634).
- For hyperviscosity syndrome, a centrifugation system is required, rather than a plasma filter (➡ Hyperviscosity syndrome, p. 654).
- For lipopheresis, there may be severe reactions if the patient is on an ACEI.
- An alternative to plasmapheresis is immunoabsorption, in which two columns are used in parallel. This may be used in the removal of HLA antibodies, anti-GBM disease, or multisystem vasculitis.

Renal biopsy

Indications

Biopsy is now performed using real-time US guidance by trained doctors (see Box 15.6).

Contraindications

- Bleeding diathesis—unless correctable prior to biopsy.
- Solitary functioning kidney.
- Uncontrolled hypertension, i.e. DBP >100mmHg.
- Urinary tract obstruction.
- Small kidneys, since it is unlikely to be helpful.

Prior to biopsy

- Check Hb, clotting screen, G&S serum.
- Ensure IVU or USS has been carried out to determine the presence and size of the two kidneys.
- Consent the patient; >1% risk of bleeding requiring transfusion.

Technique

- The biopsy is taken with the patient prone on the bed, with pillows under the abdomen. The lower pole of either kidney is visualized by US. A trucut biopsy is taken from the lower renal pole under sterile conditions with local anaesthesia. The biopsy is taken with the patient holding their breath at the end of inspiration (displaces the kidney inferiorly). Following biopsy, they should have bed rest for 24h to minimize the risk of bleeding, and the BP and pulse monitored half-hourly for 2h, 1-hourly for 4h, then 4-hourly for 18h.
- Send renal biopsy tissue for light microscopy, immunofluorescence, EM, and special stains (e.g. Congo red).

Complications

- Bleeding: microscopic haematuria is usual; macroscopic haematuria in 5–10%; bleeding requiring transfusion in 1%.
- Formation of an intrarenal arteriovenous fistula may occur.
- Severe loin pain suggests bleeding.
- Pneumothorax and ileus are rare.

Renal transplant biopsy

Indications

- Decline in transplant function.
- Primary non-function post-transplant.

Procedure

Biopsy may be taken from either the upper or the lower pole. Some centres find fine-needle aspiration biopsy (FNAB) useful in the diagnosis of transplant rejection.

Box 15.6 Indications for renal biopsy

- Cause is unknown.
- Heavy proteinuria (>2g/day).
- Features of systemic disease.
- Active urinary sediment.
- Immune-mediated ARF.
- Prolonged renal failure (>2 weeks).
- Suspected interstitial nephritis (drug-induced).

pH_i determination (gastric tonometer)

Patients in shock have reduced splanchnic perfusion and O₂ delivery. The resulting mucosal ischaemia may be difficult to diagnose clinically until it presents as GI bleeding or the sepsis syndrome. The earliest change detectable following an ischaemic insult to the gut is a fall in intramucosal pH. Gastric mucosal pH parallels the changes in pH in other portions of the GIT, and monitoring this allows detection of gut ischaemia early.

A tonometer is essentially an NG tube with a second lumen leading to a balloon which lies within the mucosal folds of the stomach. The balloon is inflated with 0.9% saline for 30–90min. This allows CO₂ from the mucosa to diffuse into the saline and equilibrate. The saline is then removed and analysed for pCO₂, with simultaneous arterial blood [bicarbonate] measurement. pH_i is then calculated using a modification of the Henderson–Hasselbalch equation.

Joint aspiration

Many synovial joints can be safely aspirated by an experienced operator. Knee effusions are common, and aseptic aspiration can be safely performed in the emergency department. The risk of inducing septic arthritis is <1 in 10 000 aspirations, but certain rules should be followed:

- Anatomical landmarks are identified.
- The skin is cleaned with alcohol or iodine.
- Local anaesthetic is applied to the area.
- A no-touch technique is essential.
- Aspirate the joint to dryness, by leaving the needle in the joint space and changing syringes.

Indications for synovial fluid aspiration in casualty

- Suspected septic arthritis.
- Suspected crystal arthritis.
- Suspected haemarthrosis.
- Relief of symptoms by removal of effusion in degenerative arthritis.

Contraindications to joint aspiration

- Overlying sepsis—never insert a needle through an area of cellulitis, as there is a risk of introducing infection into the joint.
- Bleeding diathesis.
- Prosthetic joints—must be aspirated in theatre by the orthopaedic surgeons

Knee joint

The patient lies with the knee slightly flexed and supported. The joint space behind the patella either medially or laterally is palpated, the skin cleaned, and a needle (18G, green) inserted horizontally between the patella and the femur using a no-touch technique. There is a slight resistance, as the needle goes through the synovial membrane. Aspirate on the syringe until fluid is obtained. (See Fig. 15.15a, b.)

Elbow joint

Flex the elbow to 90°, and pass the needle between the proximal head of the radius (locate by rotating the patient's hand) and the lateral epicondyle; or the needle can be passed posteriorly between the lateral epicondyle and the olecranon. (See Fig. 15.15c.)

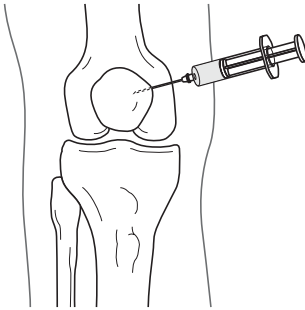
Ankle joint

Plantarflex the foot slightly; palpate the joint margin between the extensor hallucis longus (lateral) and the tibialis anterior (medial) tendons just above the tip of the medial malleolus. (See Fig. 15.15d.)

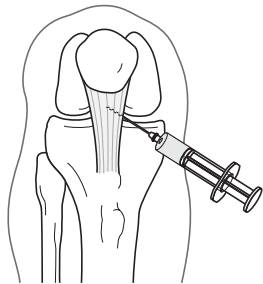
When synovial fluid is obtained:

- Note the colour and assess the viscosity.
- Microscopy for cell count and crystals (see Table 15.3).
- Gram stain and culture.
- AFB for suspected TB (although synovial fluid is usually non-diagnostic, and a synovial biopsy should be performed).

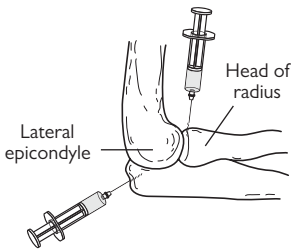
(a) Right knee, extended



(b) Right knee, flexed



(c) Right elbow, flexed



(d) Dorsal view of right ankle

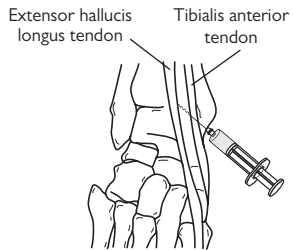


Fig. 15.15 Approaches used for joint aspiration. After Crawley M (1974). *Br Hosp Med* 11:747–55.

Table 15.3 Synovial fluid analysis

Condition	Viscosity	Opacity	Leucocyte count (per mm ³)
Normal	High	Clear	<200
Osteoarthritis	High	Clear	1000 (<50% PMN)
Rheumatoid	Low	Cloudy	1–50 000 PMN
TB	Low	Cloudy/clear	10–20 000 (poly-/mononuclear)
Crystal	Low	Cloudy	5–50 000 PMN
Sepsis	Low	Cloudy	10–100 000 PMN

Intracranial pressure monitoring

Indications

- Cerebral trauma (GCS score ≤ 8 , compression of the basal cistern on CT, midline shift of $>0.5\text{mm}$ on CT, non-surgical raised ICP).
- Acute liver failure (grade 4 coma with signs of raised ICP).
- Metabolic diseases with raised ICP (e.g. Reye's syndrome).
- Post-operative oedema (after neurosurgery).
- After an intracranial haemorrhage (SAH or intracerebral).

ICP monitoring should be started before secondary brain injury in patients who are at risk of sudden rises in ICP and where it would influence management of the patient. These patients may be effectively managed in district hospitals.

Contraindications

- Uncorrectable coagulopathy.
- Local infection near the placement site or meningitis.
- Septicaemia.

Method

- There are several types of devices available (subdural, extradural, parenchymal, or intraventricular); parenchymal and intraventricular monitors carry a high risk.
- There are prepackaged kits available (e.g. the Codman[®] subdural bolt). This monitor is inserted in the prefrontal region, and the kit contains the necessary screws for creating a burr-hole, spinal needles to perforate the dura, etc.
- The ICP waveform obtained is a dynamic recording that looks similar to a pulse waveform, and is due to pulsations of the cerebral blood vessels within the confined space of the cranium, together with the effects of respiration.
- Cerebral perfusion pressure = MAP – ICP.
- The normal resting mean ICP measured in a supine patient is $<10\text{mmHg}$ ($<1.3\text{kPa}$).
- The level which requires treatment depends, to some extent, on the disease—in benign intracranial hypertension, values of $>40\text{mmHg}$ may not be associated with neurological symptoms; but in patients with cerebral trauma, treatment should be initiated when the ICP is $>25\text{mmHg}$.
- There are several types of pressure waves described, of which the most significant are 'A waves'—sustained increases of the ICP lasting 10–20min up to 50–100mmHg (6–13kPa). These are associated with a poor prognosis.
- Readings of the ICP monitors should always be accompanied by careful neurological examination.
- Treatment of raised ICP is discussed under ➡ Raised intracranial pressure, pp. 388–90.

Complications

- Infection (up to 5%).
- Bleeding (local, subdural, extradural, or intracerebral).
- CSF leak.
- Seizures.
- Misreading of ICP.

Lumbar puncture 1

Contraindications

- Raised ICP (falling level of consciousness with falling pulse, rising BP, vomiting, focal signs, papilloedema). A CT scan should be carried out prior to an LP to exclude an obstructed CSF system or SOL (➡ Raised intracranial pressure, pp. 388–90).
- Coagulopathy or ↓ platelets ($<50 \times 10^9/L$).

You will need

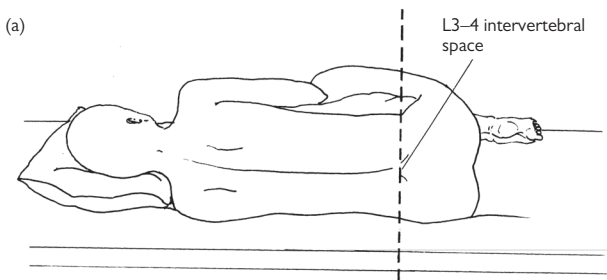
- Spinal needles and a manometer for measuring the opening CSF pressure.
- Dressing pack (gauze, drapes, antiseptic, gloves, plaster).
- Local anaesthetic (e.g. 2% lidocaine), three sterile bottles for collecting CSF, and a glucose bottle.

Procedure

(See Fig. 15.16.)

Give antibiotics first if suspected meningitis (➡ Acute bacterial meningitis: assessment, p. 371).

- Explain the procedure to the patient.
- Position the patient. This is crucial to success. Lie the patient on their left side if you are right-handed or on their right side if you are left-handed, with their back on the edge of the bed, fully flexed (knees to chin), with a folded pillow between their legs, keeping the back perpendicular to the bed. Flexion separates the interspaces.
- The safest site for LP is the L4–L5 interspace (the spinal cord ends at L1–L2). An imaginary line drawn between the iliac crests intersects the spine at the L4 process or L4–L5 space exactly. Mark the L4–5 intervertebral space.
- Clean the skin, and place the sterile drapes over the patient.
- Inject and anaesthetize the deep structures with 2% lidocaine.
- Insert the spinal needle (stylet in place) in the midline, aiming slightly cranially (towards the umbilicus), horizontal to the bed. Do not advance the needle without the stylet in place.
- You will feel the resistance of the spinal ligaments, and then the dura, followed by a 'give' as the needle enters the subarachnoid space. Replace the stylet before advancing.
- Measure the CSF pressure with the manometer and 3-way tap. Normal opening pressure is 7–20cmCSF. CSF pressure is ↑ with anxiety, SAH, infection, SOL, benign intracranial hypertension (BIH), and CCF.
- Collect 0.5–1.5mL of fluid in three serially numbered bottles, including a glucose bottle.
- Send specimens promptly for microscopy, culture, protein, glucose (with a simultaneous plasma sample for comparison), and, where appropriate, virology, syphilis serology, cytology for malignancy, AFB, oligoclonal bands (MS), CrAg, India ink stains, and fungal culture.
- Remove the needle, and place a plaster over the site.
- The patient should lie flat for at least 6h and have hourly neurological observations and BP measurements.



Position the patient so that the line joining the iliac crests is perpendicular to the bed.



Ask the patient to curl up with a pillow between the knees to open the interspace. Point the needle cranially and advance gently.

Fig. 15.16 Lumbar puncture.

Lumbar puncture 2

Complications of lumbar puncture

- **Headache:** common (up to 25%). Typically present when the patient is upright and better when supine. May last for days. Thought to be due to CSF depletion from a persistent leak from the LP site. Prevented by using finer spinal needles; keep the patient supine for 6–12h post-LP, and encourage fluids. Treat with analgesia, fluids, and reassurance.
- **Trauma to nerve roots:** rarer, but seen if the needle does not stay in the midline. The patient experiences sharp pains or paraesthesiae down the leg. Withdraw the needle, and if the symptoms persist, stop the procedure and seek expert help.
- **Bleeding:** minor bleeding may occur with a 'traumatic tap' when a small spinal vein is nicked. The CSF appears bloody (see ➡ CSF analysis, p. 858), but the bleeding stops spontaneously and does not require specific therapy. Coagulopathy, severe liver disease, or thrombocytopenia carries the risk of subarachnoid/subdural bleeding and paralysis.
- **Coning:** herniation of cerebellar tonsils with compression of the medulla is very rare, unless the patient has raised ICP. Always get a CT brain scan prior to LP, and review this yourself if possible. Mortality is high, but the patient may respond to standard measures for treating this (➡ Raised intracranial pressure, pp. 388–90).
- **Infection:** rare if a proper sterile technique used.

CSF analysis

(See Table 15.4.)

- **Normal values:**
 - Lymphocytes $<4/\text{mm}^3$; polymorphs $0/\text{mm}^3$.
 - Protein $<0.4\text{g/L}$.
 - Glucose $>2.2\text{mmol/L}$ (or $>70\%$ plasma glucose).
 - Opening pressure $<20\text{cmCSF}$.
- A **bloody tap** is indicated by progressively fewer red cells in successive bottles and no yellowing of CSF (xanthochromia). The true WCC may be estimated by:

$$\text{True CSF WCC} = \text{CSF WCC} - (\text{blood WCC} \times \text{CSF RBC}) / \text{blood RBC}$$
- If the patient's blood count is normal, subtract ~ 1 WBC for every 1000 RBCs). To estimate the true protein level, subtract 10mg/L for every $1000 \text{ RBCs}/\text{mm}^3$ (be sure to do the count and protein estimation on the same bottle).
- **SAH:** (➡ Subarachnoid haemorrhage: assessment, p. 402) xanthochromia (yellowing of CSF); red cells in equal numbers in all bottles. The RBCs will excite an inflammatory response (increasing CSF WCC), most marked after 48h.
- **Very high CSF protein:** a marked increase in CSF protein—acoustic neuroma and spinal tumours; GBS (➡ Guillain–Barré Syndrome, pp. 452–3).

Table 15.4 CSF analysis

	Bacterial	Viral	TB meningitis
Appearance	Turbid	Clear	Clear
Cells (mm ³)	5–2000	5–500	5–1000
Main cell type	Neutrophil	Lymphocyte	Lymphocyte
Glucose (mmol/L)	Very low	Normal	Low
Protein (g/L)	Often >1.0	0.5–0.9	Often >1.0
Other tests	Gram stain	PCR	ZN
	Bacterial Ag		Fluorescence test PCR

Needle-stick injuries

Occupational exposures to bloodborne viruses (BBVs) in health-care workers can be divided into two groups: percutaneous (needle-stick) and mucocutaneous (e.g. through broken skin or via splashes into the eyes). High-risk body fluids include: blood, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid, amniotic fluid, human breast milk, CSF, saliva (in dentistry), semen, vaginal secretions, and unfixed tissues and organs (vomit, faeces, and urine only when contaminated with blood).

The major pathogens associated with needle-stick injuries and mucocutaneous exposures are:

- HBV.
- HCV.
- HIV.

Occupational exposures to BBVs can be caused by certain work practices such as:

- Not properly disposing of used needles.
- Recapping needles.
- Not using protective equipments, e.g. eye protection.

Prevention

Assume that every patient is potentially infected with a bloodborne infection. The same precautions should be taken for every patient and every procedure.

- Cover skin cuts and abrasions with waterproof dressings.
- Never recap needles or pass sharps hand to hand.
- Always dispose of used needles promptly in sharps disposal containers at the point of use.
- Never leave sharps to be cleared up by others.
- Use eye protection. Ordinary spectacles offer inadequate protection. Use safety glasses, which fit over spectacles.
- Double-gloving reduces the risk of BBV transmission from a sharp injury.
- Use safer sharp devices; according to Health and Safety (Sharp Instruments in Healthcare) Regulations 2013: 'the employer must substitute traditional, unprotected sharps with a "Safer Sharp" where it reasonably practicable to do so'.

Management of exposure incidents

- If the mouth or eyes are involved, wash thoroughly with water.
- If the skin is punctured, let the wound bleed and wash it with soap and water.
- Report to the occupational health department to arrange immediate assessment or, if out of hours, attend the A&E department.

Assessment of the risk of bloodborne virus transmission

Estimated seroconversion risks are:

- *HBV*: 30% for percutaneous exposure of a non-immune individual to HBsAg- and HBeAg-positive source.
- *HCV*: 1.9% for percutaneous exposure to HCV-infected blood with detectable HCV RNA.
- *HIV*: 0.3% for percutaneous exposure to HIV-infected blood.

Factors increasing the risk following injury include

- Percutaneous injury is higher risk than mucous membrane or broken skin exposure.
- Injury with a device directly from a source patient's artery/vein.
- Injury from hollow-bore and wide-gauge needles.
- Deep injury.
- Visible blood on the device.
- High HIV viral load, or HBeAg in the source patient.
- Staff member inadequately immunized against hepatitis B.

Approaching source patients for bloodborne virus testing

- Due to the sensitivity of the issue, the source patient should not be approached by the exposed member of staff.
- Occupational health (or A&E if out of hours) will arrange this test.

Post-exposure prophylaxis for HIV

(See Box 8.4.)

- Risk assessment is carried out by occupational health (A&E if out of hours).
- PEP should be initiated as soon as possible—ideally within an hour, and generally within 72h of exposure, and continued for 28 days.
- Follow-up is carried out by occupational health, in accordance with local policy.

PEP for HBV

PEP for hepatitis B following significant occupational exposure depends on if the recipient has been immunized against hepatitis B and if adequate immunity has been achieved. Risk assessment is carried out by occupational health (A&E if out of hours).

PEP for HCV

Although there is no vaccine or effective PEP against hepatitis C, evidence suggests that early treatment can result in viral clearance in up to 80% of the cases. This emphasizes the importance of close and timely follow-up of exposed workers.

Differential diagnosis of common presentations

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Introduction

It is often said that 80% of the diagnosis depends on a good history. The differential diagnosis formed from the history can then be narrowed down by physical examination and investigations.

The history of the presenting complaint is a key component of establishing a diagnosis and should be divided into three subsections to ensure that the most crucial points in the history are dealt with at an early stage.

About the symptom

That is, what, where (including radiation), when (onset, duration, course), how bad (severity), exacerbating/relieving factors, etc.

About the most relevant organ system

(For example, questions relating to the respiratory and cardiovascular systems for a patient presenting with breathlessness.) It is important to ask about the most relevant organ systems and common 'associated symptoms' during the initial history, rather than during the systemic enquiry. See

➡ Systemic enquiry, p. 865 for a summary of the most important questions.

Risk factors

Go through your list of differential diagnoses for the presenting complaint (see next sections), and ask questions about the various differentials and risk factors that increase the likelihood of their development. For example, if a patient presents with diarrhoea, the list of differential diagnoses includes infection. Therefore, risk factors such as contacts, food history, recent travel, etc. should be addressed.

The following pages will outline relatively short/memorable lists of differential diagnoses for the most common presenting symptoms. These lists are not comprehensive but are a good starting point. Each list of differential diagnoses can be used as a guide for asking the important questions about each differential and the risk factors.

See the appropriate sections in the rest of this book for further information on the clinical signs and the specific investigations needed to exclude or confirm a diagnosis.

Systemic enquiry

General questions

Fever, sweats, fatigue, malaise, loss of appetite, weight loss, lumps.

Cardiovascular

Chest pain, palpitation, breathlessness (exertional, at rest, orthopnoea, paroxysmal nocturnal dyspnoea), ankle swelling, dizziness.

Respiratory

Wheeze, breathlessness, cough, sputum, haemoptysis, chest pain, calf pain/swelling.

Gastrointestinal

Loss of appetite/weight, nausea/vomiting, dysphagia, indigestion/heartburn, abdominal pain, change of bowel habit (diarrhoea or constipation), bloating, blood/mucus PR, melaena or haematemesis, jaundice, pruritus, dark urine, pale stool.

Urogenital

Urinary frequency, urgency, dysuria, haematuria, loin pain, vaginal/penile discharge, periods/sexual problems.

Neurological

Cognitive impairment or reduced consciousness (from collateral history), visual disturbance, hearing loss, speech/swallowing problems, headache, neck/back pain, weakness, paraesthesiae, balance/coordination problems, bowel/bladder control.

Rheumatological

Morning stiffness, joint pain/swelling/stiffness, deformity, malaise/fatigue/weight loss, arthralgia, myalgia, rash, Raynaud's phenomenon, hair loss, red or sore or dry eyes, dry mouth, oral ulcers, genital ulcers.

Diabetes and endocrine

Polyuria, polydipsia, fatigue, weight loss, neck swelling or tenderness, tremor, heat/cold intolerance, sweating, changes in hair, skin, voice, face, hands, or feet appearance, pigmentation.

Ear, nose, and throat

Ear pain/discharge, nasal discharge/crusting, sore throat.

Abdominal pain 1

(See Fig. 16.1.)

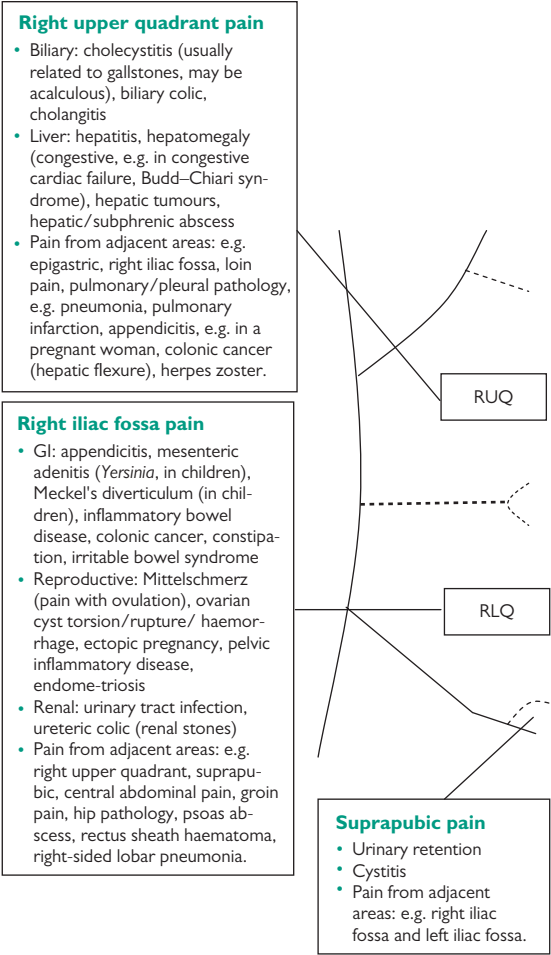


Fig. 16.1 Causes of regional abdominal pain.

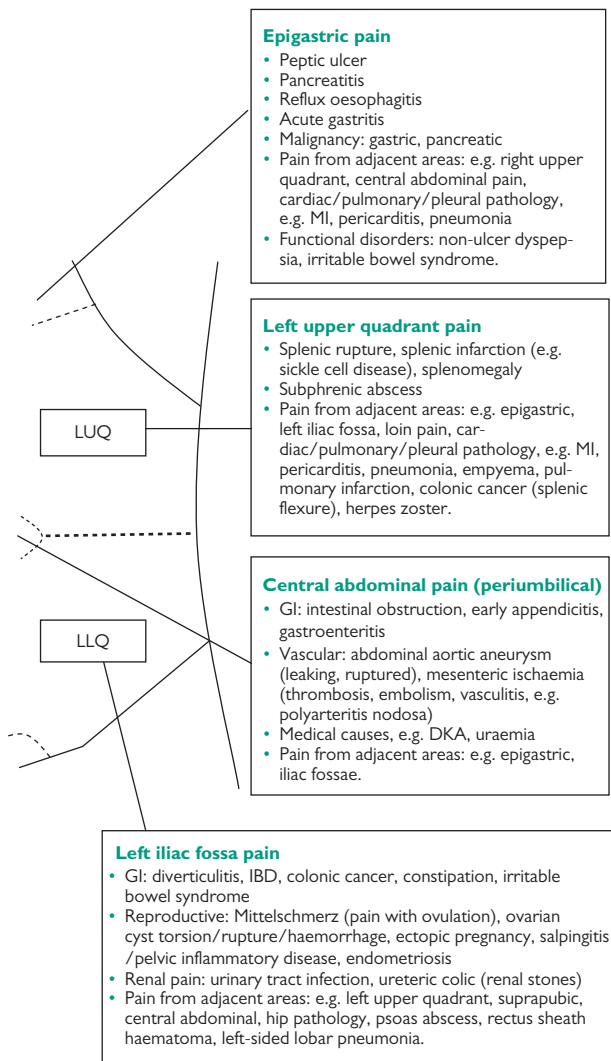


Fig. 16.1 (Contd.)

Abdominal pain 2

Loin pain

- Infection: UTI (pyelonephritis), perinephric abscess/pyonephrosis.
- Obstruction: in the lumen, e.g. stones, tumour, blood clots; in the wall, e.g. stricture (ureteric/urethral); pressure from the outside, e.g. prostatic/pelvic mass, retroperitoneal fibrosis.
- Other: renal carcinoma, renal vein thrombosis, polycystic kidney disease, pain from the vertebral column.

Groin pain

- Renal stones (pain radiating from loin to groin).
- Testicular pain, e.g. torsion, epididymo-orchitis (pain radiating from scrotum to groin). Hernia (inguinal), hip or pelvic pathology, e.g. fracture.

Diffuse abdominal pain

- Gastroenteritis.
- Peritonitis.
- Intestinal obstruction.
- IBD.
- Mesenteric ischaemia.
- Medical causes.
- Irritable bowel syndrome.

Medical causes

Most causes of abdominal pain are surgical. However, occasionally there may be a 'medical cause' of abdominal pain:

- Cardiovascular/respiratory: MI, pneumonia, Bornholm's disease (Coxsackie B virus infection).
- Metabolic: DKA, Addisonian crisis, hypercalcaemia, uraemia, porphyria, pheochromocytoma, lead poisoning.
- Neurological: herpes zoster.
- Haematological: sickle-cell crisis, retroperitoneal haemorrhage (e.g. anticoagulants), lymphadenopathy.
- Inflammatory: vasculitis (e.g. Henoch–Schönlein purpura, PAN), familial Mediterranean fever.
- Infections: intestinal parasites, TB, malaria, typhoid fever.
- Irritable bowel syndrome.

Abdominal pain (referred)

(See Fig. 16.2.)

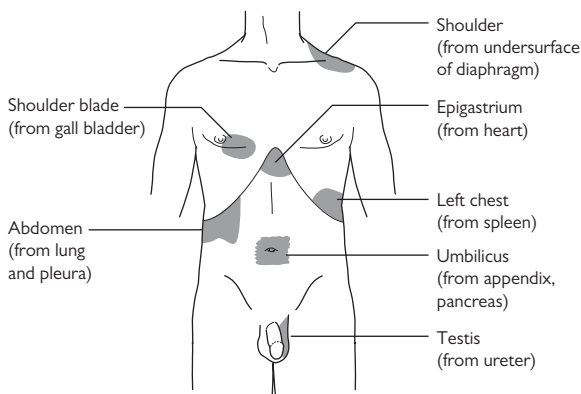


Fig. 16.2 Common sites of referred pain.

Abdominal distension

- Fat (obesity).
- Fluid (ascites, fluid in the obstructed intestine).
- Flatus (intestinal obstruction).
- Faeces.
- Fetus.
- Giant organomegaly (e.g. ovarian cystadenoma, lymphoma).
- Small bowel: adhesions, herniae, Crohn's disease, gallstone ileus, foreign body, tumour, TB.
- Large bowel: cancer, volvulus, diverticulitis, faeces.

Back pain

All patients

- Strenuous activity, muscle spasm, trauma, fractures.
- Infection: TB or bacterial osteomyelitis of vertebra, discitis.
- Malignancy: metastasis, multiple myeloma, malignant lumbosacral plexopathy (with colorectal and gynaecologic tumours, sarcomas, lymphomas).
- Spinal cord compression.
- Infection: epidural abscesses (IV users, vertebral osteomyelitis, haematogenous spread)—common pathogens: *Staphylococcus aureus*, *Mycobacterium tuberculosis*.
- Malignancy: myeloma, metastases (vertebral, spinal cord).
- Inflammatory: RA, sarcoidosis, or tophaceous gout.
- Other: haematomas (bleeding disorders, anticoagulant therapy), arteriovenous malformation.

Younger patients (≤ 40 year)

- Prolapsed disc, ankylosing spondylitis, spondylolisthesis.

Older patients (≥ 40 year)

- Osteoarthritis, spinal stenosis, and spinal claudication.
- Osteoporotic fractures, Paget's disease of bone.

Blackouts

Cardiovascular (due to transient reduction in blood flow to the brain)

- Arrhythmia: bradycardia (heart block), tachycardia.
- Outflow obstruction: aortic stenosis, hypertrophic obstructive cardiomyopathy, PE, pulmonary stenosis.
- Postural hypotension: hypovolaemia, autonomic neuropathy (e.g. DM), antihypertensive medications (e.g. ACEIs).
- MI, aortic dissection, and any other condition that may cause a sudden reduction in cardiac output.

Neurological

- Epilepsy, stroke/TIA (rarely).

Neurocardiogenic (vasovagal) syncope and carotid sinus hypersensitivity

Vasovagal syncope may be induced by prolonged standing, cough, micturition, venepuncture, heat exposure, or painful stimuli. There may be no identifiable cause, especially in the elderly. Blackouts due to carotid sinus hypersensitivity may be produced by head turning, tight-fitting collars, or shaving.

Metabolic

- Hypoglycaemia (⊕ Hypoglycaemia: assessment, pp. 556–7).

Breathlessness/dyspnoea

The causes of breathlessness are best classified according to rapidity of onset. However, although the onset gives a significant clue, the following lists are not mutually exclusive.

Acute (seconds)

- PE.
- Pneumothorax.
- Foreign body.
- Anaphylaxis.
- Anxiety.

Subacute (minutes to hours)

- Acute LVF (pulmonary oedema).
- Asthma exacerbation.
- COPD exacerbation.
- Pneumonia (bacterial, viral, fungal, TB).
- Metabolic acidosis.

Chronic (days to weeks)

- Anaemia.
- Thyrotoxicosis.
- Recurrent PEs.
- Cardiac disease (chronic cardiac failure, arrhythmias, valvular heart disease).
- Asthma.
- COPD.
- Non-resolving pneumonia.
- Bronchiectasis.
- Lung cancer.
- Interstitial lung disease/pulmonary fibrosis (cryptogenic, connective tissue diseases, drugs, environmental/occupational lung disease).
- Pulmonary hypertension.
- Pleural effusion.
- Neuromuscular disorders, chest wall deformities.

Chest pain

Some causes of chest pain

Chest wall

- Ribs: fracture or neoplasm.
- Intercostal muscle: spasm, inflammation (Bornholm's disease).
- Costochondritis.
- Herpes zoster.
- Thoracic vertebral pain.
- Thoracic nerve root pain.

Pleura

- Pleurisy (infectious, neoplastic, vasculitic, irritative).

Lung vasculature

- Pulmonary infarction.
- Pulmonary hypertension.

Mediastinal structures

- Lymph nodes (lymphoma, cancer).
- Oesophagitis.
- Aortic dissection.
- Tracheobronchitis.
- Pericarditis.
- Myocardial pain (angina, ACS).

Extrathoracic

- Cervical arthritis.
- Subdiaphragmatic disease (e.g. hepatitis, splenic infarction, pancreatitis, peptic ulcer, gallstones).
- Migraine.

Chest pain (pleuritic)

- PE.
- Pneumothorax.
- Pneumonia.
- Pericarditis.
- Serositis/connective tissue disease.
- Malignancy involving the pleura.
- Pathology under the diaphragm.
- Musculoskeletal.

Collapse

See  Blackouts, p. 870.

Confusion

- Hypoglycaemia.
- Hypoxia: cardiac arrest, shock (hypovolaemic, septic), respiratory failure.
- Vascular: intracranial haemorrhage/infarction.
- Infection: extracranial (most commonly UTI and pneumonia in the elderly); intracranial (meningitis, encephalitis).
- Inflammation (cerebral vasculitis).
- Trauma (head injury).
- Tumour ($\uparrow$ ICP).
- Toxic: drugs, e.g. opiates, alcohol, anxiolytics, antidepressants.
- Metabolic: liver failure, renal failure, electrolyte (Na^+ , K^+ , Ca^{2+} , Mg^{2+}) disturbances, endocrinopathies, e.g. myxoedema coma, vitamin deficiencies (e.g. thiamine, B_{12}), hypothermia.
- Post-ictal.

Constipation

- Drugs: opiates, anticholinergics (tricyclics, phenothiazines), iron tablets.
- Immobility, old age.
- GI/surgical.
- Intestinal obstruction (strictures, IBD, cancers, diverticulosis, pelvic mass, e.g. fibroids).
- Pseudo-obstruction in scleroderma.
- Anorectal disease (fissure, stricture, rectal prolapse).
- Post-operative.
- Endocrine: hypothyroidism, hypercalcaemia, hypokalaemia, porphyria, lead poisoning.
- Neurological/neuromuscular: autonomic neuropathy, spinal/pelvic nerve injury, Hirschsprung's disease, Chagas' disease.

Cough

- URTI.
- All lung diseases:
 - Asthma, COPD, PEs, infection (viral/bacterial/fungal/TB pneumonia), bronchiectasis, malignancy, interstitial lung disease, sarcoidosis, pneumoconiosis.
- Other causes:
 - Post-nasal drip.
 - Gastro-oesophageal reflux disease.
 - ACEIs.
 - Cardiac failure.
 - Psychogenic.

Cutaneous manifestations of internal malignancy

Cutaneous malignancy with frequent internal spread

- Melanoma.
- Scar-related squamous cell carcinoma (e.g. mucosal surfaces, old scars).
- Mycosis fungoides.
- KS.

Internal malignancy with cutaneous spread

- Breast carcinoma.
- Leukaemia and lymphoma cutis.
- Miscellaneous (occasionally seen with GI, genitourinary, and lung malignancy).

Pigmentation changes

- Hyperpigmentation (especially with melanoma).
- Acanthosis nigricans (especially gastric cancer).
- Sign of Leser–Trélat (rapid appearance of multiple seborrhoeic keratoses).
- Peutz–Jeghers syndrome.
- Jaundice (biliary tract tumours, pancreas, liver metastases from other tumours).
- Purpura (e.g. leukaemia).

Flushing and facial erythema

- Carcinoid.
- Mastocytosis.
- Pheochromocytoma.
- Cushing's disease.

Specific skin signs sometimes associated with malignancy

- Dermatomyositis in adults.
- Bullous disease in adults (pemphigus and pemphigoid).
- Bowen's disease on non-sun-exposed areas.
- Arsenic keratosis of palms and soles.
- Paget's disease of the nipple.
- Basal cell naevus syndrome.
- Acquired ichthyosis (lymphomas).
- Exfoliative erythrodermatitis.

Diarrhoea

Infection

- **Viral:** adenovirus, astrovirus, calciviruses (norovirus and related viruses), rotavirus.
- **Bacterial:** *Campylobacter*, *Salmonella*, *Shigella*, haemorrhagic *Escherichia coli*, *Clostridium difficile*, *Yersinia enterocolitica*, *Clostridium perfringens*, *Vibrio cholerae*, *Vibrio parahaemolyticus*.
- **Parasites:** cryptosporidia, *Giardia*, *Entamoeba histolytica*.
- **AIDS:** AIDS enteropathy, cryptosporidia, microsporidia, CMV.
- **IBD.**
- **Malabsorption:** small intestine disease/resection, biliary or pancreatic disease.
- **Medication:** laxatives, antibiotics.
- **Overflow diarrhoea:** secondary to constipation.
- **Endocrine:** thyrotoxicosis, VIPomas.

NB *Staphylococcus aureus* and *Bacillus cereus* mainly present with vomiting 1–6h after ingestion of prepared food, e.g. salad, dairy, meat (*S. aureus*) and rice and meat (*B. cereus*).

Diarrhoea (bloody)

- **Infective colitis:** *Campylobacter*, haemorrhagic *E. coli*, *Salmonella*, *Shigella*, *E. histolytica*, CMV in the immunocompromised.
- **IBD.**
- **Ischaemic colitis.**
- **Diverticulitis.**
- **Malignancy.**

Dysphagia

Mechanical obstruction of the oesophagus

- Congenital stricture.
- Corrosive stricture.
- Foreign body.
- Carcinoma of the oesophagus or stomach.
- External compression (e.g. aortic aneurysm).
- Oesophageal divertula or pouch.
- Reflux oesophagitis with stricture.

Dysphagia secondary to pain

- Pharyngitis.
- Laryngitis.

Neurologic dysfunction of the oesophagus

- Bulbar paralysis.
- Syphilis.
- Lead poisoning.
- Tetanus.
- Rabies.
- Parkinson's disease.
- Botulism.
- Myasthenia gravis.
- Achalasia.
- Plummer–Vinson syndrome.
- Hysteria.

Falls

- Sensory (visual, hearing, proprioception) impairment.
- Gait/balance problem.
- Muscle weakness/rigidity.
- Urinary incontinence/frequency/urgency.
- Medications: psychotropic, opiates.
- Cognitive impairment.
- Home hazards (especially in the elderly).

Fever

- Infection: abscesses (e.g. subphrenic, liver, pelvis); bacterial— infective endocarditis, pneumonia, UTI, biliary infection, osteomyelitis, TB, brucellosis, viral (e.g. HIV, CMV, EBV), malaria, etc.
- Inflammation/connective tissue disease: e.g. RA, SLE, sarcoidosis, vasculitides, polymyalgia rheumatica.
- Malignancy: lymphomas, leukaemia, renal cell, hepatocellular, or pancreatic carcinoma.
- Metabolic: thyrotoxicosis.
- Drugs: e.g. antibiotics, allopurinol, phenytoin, interferon.
- NMS, malignant hyperthermia, serotonin syndrome.
- Familial Mediterranean fever, familial periodic fever.

Fever in a traveller

- Hepatitis A.
- Malaria.
- Dengue.
- Typhoid.
- Leptospirosis.
- Haemorrhagic fevers.
- Long incubation: malaria, typhoid, TB, brucellosis, leishmaniasis, amoebic abscess.

Fits

- Vascular: haemorrhage, infarction, cortical venous thrombosis, vascular malformation.
- Trauma: head injury.
- Tumours.
- Toxic: alcohol, drugs, lead, CO.
- Metabolic: hypoxia, hypoglycaemia, electrolyte disturbances ($\uparrow$ or $\downarrow$ Na^+ , K^+ , Ca^{2+} , Mg^{2+}), renal/hepatic failure, endocrine disorders (e.g. myxoedema), vitamin deficiency.
- Infection: meningitis, encephalitis, abscess, TB, cysticercosis, HIV.
- Inflammation: MS, vasculitis, SLE, sarcoidosis.
- Malignant hypertension.

Haematemesis and melaena

- Peptic ulcer (gastric/duodenal).
- Gastritis/gastric erosions, duodenitis, oesophagitis.
- Gastro-oesophageal varices.
- Mallory–Weiss tear.
- Medications: NSAIDs, anticoagulants, steroids, thrombolytics.
- Oesophageal/gastric cancer.
- Rarely: bleeding disorders (thrombocytopenia, haemophilia), hereditary haemorrhagic telangiectasia, Dieulafoy gastric vascular abnormality, aortoduodenal fistulae, angiodysplasia, leiomyoma, Meckel's diverticulum, pseudoxanthoma elasticum.

Haematuria

(See Fig. 16.3.)

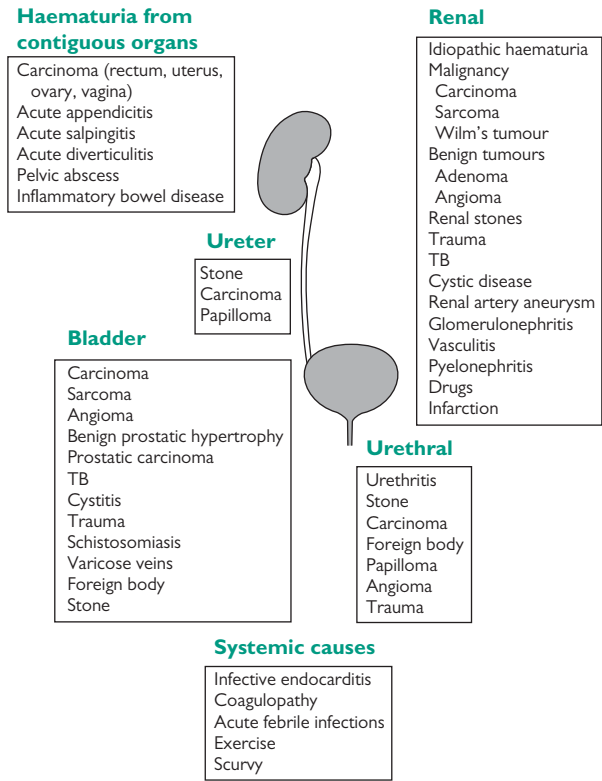


Fig. 16.3 Causes of haematuria.

Haemoptysis

NB Nasal or upper respiratory tract and GI bleeding may be confused with haemoptysis

Infectious

- Acute bronchitis.
- Pneumonia.
- Bronchiectasis.
- Lung abscess.
- Mycobacterial infection.
- Fungal infection (histoplasmosis, coccidiomycosis, aspergillosis).
- Parasites (paragonimiasis, schistosomiasis, ascariasis, amoebiasis, echinococcus, strongyloidiasis, etc.).

Neoplastic

- Bronchogenic carcinoma.
- Bronchial adenoma.
- Metastatic deposits.

Traumatic

- Lung contusion.
- Bronchial rupture.
- Post-endotracheal intubation.

Vascular

- Pulmonary infarction.
- Pulmonary vasculitis.
- Arteriovenous fistula.

Cardiovascular

- Pulmonary oedema.

Parenchymal

- Diffuse interstitial fibrosis.
- Systemic diseases and vasculitis (WG, RA, SLE, Goodpasture's, etc.).
- Sarcoidosis.

Headache

Serious causes to exclude

- Head injury.
- Meningitis/encephalitis.
- Vascular: haemorrhage (subarachnoid, intracranial), cerebral venous thrombosis, pituitary apoplexy.
- Dissection (carotid/vertebral artery).
- Acute angle closure glaucoma.
- Giant cell arteritis.
- Other causes: malignant hypertension, drugs (e.g. GTN, Ca²⁺ channel antagonists), infections (bacterial, viral illnesses, etc.), electrolyte imbalances (e.g. hyponatraemia), hyperviscosity syndromes (e.g. polycythaemia), reduced ICP (e.g. post-LP), migraine, migrainous neuralgia.

Hemiparesis

- Vascular: infarction, haemorrhage.
- Infection: brain abscess from local (e.g. middle ear, sinuses) or distant (e.g. lung) infections, in the immunocompromised—TB, toxoplasmosis, PML.
- Inflammation: demyelination, cerebral vasculitis.
- Trauma: extradural or subdural haemorrhage (a history of trauma may not be apparent in the latter).
- Tumours: primary (e.g. meningioma, glioma), metastases, lymphoma.
- Metabolic: hypoglycaemia (transient).
- Other causes of transient hemiparesis: epileptic seizures (Todd's paralysis), migraine.

Hoarseness

Traumatic

- Foreign body.
- External injury to the larynx.
- Voice abuse ('singer's nodules').
- Irritant gases (tobacco and other smoke).
- Aspiration (acid, alcohol).

Infections

- Viral.
- Diphtheria.
- Syphilis.
- Leprosy.

Idiopathic

- Sarcoidosis.
- Lupus erythematosus.
- Cricoarytenoid ankylosis in RA.

Neurological

- Recurrent laryngeal palsy.
- Bulbar palsy.
- Myasthenia gravis.

Other

- Weakness.
- Myxoedema.
- Acromegaly.

Itching/pruritus

Causes of pruritus with visible skin disease

Rashes with excoriation

- Eczematous diseases (atopic, contact dermatitis, stasis dermatitis, anogenital pruritus, seborrhoeic dermatitis).
- Scabies.
- Dermatitis herpetiformis.
- Psoriasis.
- Superficial fungal disease (especially feet and intertriginous areas).
- Pinworm infestation (perianal).
- Psychogenic causes.

Rashes with little or no excoriation

- Urticaria.
- EM.
- Lichen planus.
- Drug reactions.
- Pityriasis rosea.
- Urticaria pigmentosa (mastocytosis).
- Pruritic papules of pregnancy.

Causes of pruritus without visible skin disease

Associated with internal disease

- Uraemia.
- Liver disease (biliary cirrhosis, obstructive jaundice).
- Lymphoma.
- Polycythaemia.
- Pregnancy.
- Miscellaneous (e.g. occasionally seen with DM, thyroid disease, parathyroid disease, iron deficiency, internal malignancy, etc.).

Not associated with internal disease

- Pediculosis pubis.
- Pinworm infestation.
- Xerosis.
- Psychogenic.

Joint pain/swelling

Single joint

- Infection: septic arthritis (staphylococci, gonococci, Gram –ve bacilli, TB, Lyme disease).
- Trauma, haemarthrosis (haemophilia).
- Gout/pseudogout.
- RA, osteoarthritis.
- Seronegative arthritides: reactive arthritis, enteropathic arthritis (IBD, Whipple's disease), ankylosing spondylitis, psoriatic arthritis.
- Systemic: SLE, Sjögren's syndrome, sarcoidosis, Behçet's disease, vasculitides.
- Malignancy.

Multiple joints

- Infection: disseminated septic arthritis (e.g. staphylococcal, gonococcal), viral (e.g. enteroviruses, EBV, HIV, hepatitis B, mumps, rubella), rheumatic fever, Lyme disease, TB.
- Gout/pseudogout.
- RA, osteoarthritis (generalized).
- Seronegative arthritis: reactive/Reiter's, enteropathic (Whipple's, IBD), ankylosing spondylitis, psoriatic arthritis.
- Systemic diseases: SLE, sarcoid, Sjögren's, Behçet's, primary vasculitides, polymyalgia rheumatica.
- Other: haemochromatosis, sickle cell, malignancy (hypertrophic pulmonary osteoarthropathy).

Leg swelling

Bilateral

- Cardiac failure.
- Liver failure.
- Other causes of hypoalbuminaemia (malnutrition, malabsorption, nephrotic syndrome, protein-losing enteropathy).
- Renal failure.
- Hypothyroidism.
- Iatrogenic: oestrogens, Ca^{2+} channel blockers, 'glitazones', NSAIDs, fluid overload.
- Venous insufficiency: acute (prolonged sitting), chronic venous obstruction, e.g. pelvic mass, pregnancy, IVC/bilateral iliac vein obstruction.

Unilateral

- Acute.
- DVT.
- Cellulitis.
- Compartment syndrome, trauma.
- Baker's cyst rupture.

Chronic

- Varicose veins.
- Lymphoedema (non-pitting): primary, lymph node involvement [radiotherapy, infection (filariasis), malignant infiltration, excision].
- Immobility.

Melaena

See ➡ Haematemesis and melaena, p. 877.

Muscle weakness

Congenital

- Muscular dystrophies: (limb-girdle, facioscapulohumoral, Duchenne, myotonic).
- Glycogen storage diseases.
- Inherited spinal muscular atrophies.

Infectious

- Viral (e.g. influenza).
- Bacterial (e.g. TB, syphilis).
- Parasites (e.g. trichinosis, toxoplasmosis, trypanosomiasis).

Toxic

- Alcohol.
- Heavy metals (e.g. mercury, lead, arsenic).
- Corticosteroids.
- Organophosphates.
- Drugs (vincristine, doxorubicin, heroin).
- Botulism.

Traumatic

- Exercise.
- Injury.
- Seizure.

Metabolic

- Hyper- or hypothyroidism.
- Hypokalaemia.
- Hypophosphataemia.
- Hypocalcaemia..
- Hypomagnesaemia.
- Hypoglycaemia.
- DM.
- Cushing's disease.
- Addison's disease.
- Hyperparathyroidism.
- Hyperaldosteronism.
- Acromegaly.
- Malnutrition.

Vascular insufficiency

Immune/idiopathic

- Myasthenia gravis.
- Scleroderma.
- SLE.
- PAN.
- RA.
- PMR.
- Sarcoidosis.
- Polymyositis/dermatomyositis.

Neoplastic

- Carcinomatous myopathy.
- Eaton–Lambert syndrome.
- Carcinoid myopathy.

Nausea

See ➞ Vomiting, p. 888.

Palpitations

- Fever, dehydration, exercise, anaemia, pregnancy.
- Drugs (caffeine, nicotine, salbutamol, anticholinergics, vasodilators, cocaine).
- Cardiac: any arrhythmia (e.g. AF, extrasystoles, SVT, VT), valvular disease, cardiomyopathy, septal defects, atrial myxoma.
- Endocrine: thyrotoxicosis, phaeochromocytomas, hypoglycaemia, mastocytosis.
- Psychiatric: panic attacks, generalized anxiety disorder.

Seizures

See ➞ Fits, p. 877.

Tremor

See Table 16.1.

Table 16.1 Characteristics of tremor

Tremor type	Characteristics	Seen in
Simple tremor		
<i>Essential, familial, or senile tremor</i>	Not present at rest (except in the head)	Persons with family history Fatigue Advanced age Stimulants Fever Thyrotoxicosis
<i>Parkinsonism</i>	Present in the hands at complete rest Associated with rigidity; ↓ associative movements, small steppage gait, mask-like facies	Parkinsonism of all types
<i>Cerebellar tremor</i>	Worse with motion and associated with cerebellar signs	MS, Wilson's disease, hereditary ataxia
Chorea	Jerky, irregular, sudden movements, intermittent fidgeting	Acute rheumatic fever (Sydenham's chorea) Huntington's chorea
Athetosis	Upper limbs predominate Slow, sinuous, writhing movements	Cerebral palsy Drugs
Myoclonus	Sudden jerks of single muscles or groups	Epilepsy Encephalitis Hyponatraemia Hyperosmolar state Some degenerative CNS diseases
Tetanic spasms	Sustained contractions of single muscles or muscle groups	Tetanus Spasticity
Hemiballismus	Flinging movements of the arm and leg on one side	Infarction of the subthalamic nucleus

Unconsciousness/reduced consciousness

- Hypoglycaemia.
- Hypoxia: cardiac arrest, shock (hypovolaemic, septic), respiratory failure.
- Vascular: intracranial haemorrhage/infarction.
- Infection: meningitis, encephalitis.
- Inflammation (cerebral vasculitis).
- Trauma (head injury).
- Tumour (↑ ICP).
- Toxic: drugs, e.g. opiates, alcohol, anxiolytics, antidepressants.
- Metabolic: liver failure, renal failure, electrolyte (Na^+ , K^+ , Ca^{2+} , Mg^{2+}) disturbances, endocrinopathies, e.g. myxoedema coma, vitamin deficiencies (e.g. thiamine, B_{12}), hypothermia.
- Epilepsy (post-ictal).

Vomiting

- Drugs, poisoning, alcohol.
- Abdominal pathology (GI, hepatic, gynaecological).
- Metabolic/endocrine: DKA, Addisonian crisis, hypercalcaemia, uraemia, pregnancy.
- ↑ ICP (infection, SOL, BIH).
- Acute labyrinthitis.
- Acute angle closure glaucoma.

Weak legs

Spastic paraparesis

- Inflammation: demyelination, transverse myelitis (post-infectious, e.g. viral infections, *Mycoplasma*), vasculitides, sarcoidosis, SLE.
- Infection: epidural abscess, tuberculous abscess, HIV, HTLV-1 (tropical spastic paraparesis), syphilis.
- Trauma: vertebral fractures/dislocation, disc protrusion (usually spontaneous, rather than traumatic).
- Tumours: vertebral metastases, intrinsic cord tumours (ependymoma, glioma, metastases), extrinsic tumours (neurofibroma, meningioma), parasagittal meningioma.
- Metabolic: vitamin B_{12} deficiency (subacute combined degeneration).
- Degenerative: of the spine (spondylosis with cord compression); in the cord: motor neuron disease.
- Congenital: hereditary spastic paraparesis, Friedreich's ataxia.
- Other: syringomyelia

Flaccid paraparesis

- Polyneuropathies.
- Myopathies.
- Anterior spinal artery syndrome (spinal cord infarction).

Wheeze

- Angio-oedema/anaphylaxis.
- Asthma.
- Bronchitis.
- Bronchiectasis.
- Cardiac wheeze (pulmonary oedema).
- Cancer (lung).
- Carcinoid syndrome.
- Pulmonary eosinophilia.

Acute medicine and the older patient

- The older patient on the acute unit 892
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The older patient on the acute unit

At present, 65% of acute admissions to hospital are patients aged over 65,¹ with an ageing population meaning that these figures are likely to increase. Acute physicians play an important role in the care of older patients, as the majority are admitted via acute medical units. When approaching an older patient, it is key to remember that patients should not be discriminated against due to age alone and should be given equal access to beneficial interventions. There has been a move towards integrated care of older patients on acute medical units, with timely access to specialist geriatric care and education of acute physicians.

This chapter serves to equip acute physicians to treat and prevent crises in an older patient's health that may contribute to future morbidity and mortality.

It is important to remember that older patients are vulnerable to the same conditions as the younger population, as detailed throughout this book, and that the same treatments apply universally. Older patients are, however, more likely to: present with atypical or non-specific symptoms; decompensate quicker; and suffer ↑ mortality and morbidity following an acute illness. Older patients are also more likely to have multiple comorbidities and may have an extensive drug history. This needs to be taken into account when assessing and treating the acutely unwell older patient.

References

1. Cornwell J, Levenson R, Sonola L, Poteliakhoff E (2012). *Continuity of care for older hospital patients: a call for action*. The King's Fund, London.

Assessing the older patient

A full history and examination are the physician's primary tool for diagnosis and guiding focused investigation. In older patients, examination skills are the same as for the younger patient, but there are a few considerations to bear in mind:

- *Time*: the more frail patients in particular may find the process of examination tiring and some elements difficult. It may take more time to complete a full examination.
- *Pain*: may limit the examination due to underlying chronic conditions, e.g. osteoarthritis, and consideration should be given to this.
- *Non-compliance*: confusion is common, which means examination can be challenging. Often it may be useful to decide what is important to examine now, and what could be perhaps left until the environment is optimized (patients with dementia may be more compliant in the morning, for example).
- *Sensory impairment*: recognizing the need for hearing and visual aids early to aid examination.
- *PR examination*: constipation is common in elderly patients and can lead to confusion, anorexia, or pain. A PR examination should be considered.
- *Postural hypotension*: a lying and standing BP is often forgotten and can give valuable information around the fluid status and can identify the cause for falls.
- *General examination*: is the patient unkempt? Are they wearing appropriate clothing/footwear? Are there any concerns around their safety in the community, and are they likely to need support on discharge? Recognizing this early can allow for timely discharge planning.
- *Cognitive screen*: an Abbreviated Mental Test should be performed as a screen for cognitive impairment. A score of <7 prompts further investigation of impairment and a formal MMSE, Montreal Cognitive Assessment (MoCA), or Addenbrooke's Cognitive Examination-III (ACE-III).
- *Collateral history*: can often be an extremely valuable tool. Available from multiple sources—family, carers, and GP. It is useful to aim to gain this at the time of assessing.

Admission to hospital can be dangerous for older patients. They are at risk of hospital-acquired infections and hospital-acquired disability. If available, patients should be considered for ambulatory pathways and acute geriatric clinics in order to maintain independence but supply rapid, comprehensive intervention. These provide investigation and management without the risks of admission. Of course, this requires an assessment of their safety at home while unwell.

Assessing frailty

Frailty is the clinical state of ↑ vulnerability related to age-associated decline in physiological reserve. Frailty is not an inevitable part of ageing and can manifest in a variety of ways.

Be careful in judging frailty based on initial impressions and partial information—the fit older person with an acute illness, once stuck in a bed and hospital gown, looks very similar to the frail older patient in the same outfit.

In the acute setting, it is most likely that frailty will present with a ‘frailty syndrome’—an acute event that has been exacerbated by their underlying vulnerability. These syndromes can often mask a serious acute medical condition (such as MI, stroke, or sepsis). Remember that all of these ‘syndromes’ can occur in the absence of frailty.

The frailty syndromes

- Falls.
- Delirium/acute confusion.
- Reduced mobility.
- Polypharmacy/↑ susceptibility to medication side effects.
- Incontinence.
- Exacerbation of chronic conditions.

These presentations are umbrella terms encompassing a myriad of aetiologies. Frequently used unhelpful terms, such as ‘acopia’ and ‘off legs’, detract from the possibility of a serious underlying condition and should be avoided when describing a presenting complaint.

Frailty screening

Active screening can be performed in those in whom frailty is suspected, with many tests available. Frailty is best tested for in the outpatient setting, once a patient is at their ‘baseline’ function.

Examples include:

- *Timed up and go test*:² the time taken to stand up out of a chair, walk 3m and back again, with >10s suggesting frailty.
- *Gait speed*:³ <0.8m/s measured over 4–6m.
- *Frailty scores*: need to be calculated and interpreted by those trained in their use.
- *Polypharmacy*: taking >5 medications can be an indicator of frailty. Inappropriate prescribing should be looked for and medications screened for justification, net benefit, and effectiveness. (It should be noted that some conditions call for an appropriately heavier ‘pill burden’.)

References

2. Podsiadlo D, Richardson S. The timed ‘Up & Go’: a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39:142–8.
3. Abellan van Kan G, Rolland Y, Houles M, Gillette-Guyonnet S, Soto M, Vellas B. The assessment of frailty in older adults. *Clin Geriatr Med* 2010;26:275–86.

The comprehensive geriatric assessment

Frail older patients admitted should be considered for a comprehensive geriatric assessment (CGA) (see Table 17.1). This is usually performed alongside a multidisciplinary team, including physiotherapists, occupational therapists, speech and language therapists, and elderly care physicians. This ensures a holistic approach to care. Seemingly small changes in a patient's care can have a large impact on their quality of life and maintenance of their independence. This, in turn, reduces admissions, morbidity, and institutionalization.

Table 17.1 Common components of a CGA*

<i>Medical</i>	Comorbid conditions and disease severity
	Medication review
	Nutritional status
	Problem list
<i>Mental health</i>	Cognition
	Mood
<i>Functional capacity</i>	Basic activities of daily living
	Gait and balance
	Activity status
<i>Social circumstances</i>	Support available (family/friends/formal carers)
	Social network
	Eligibility for care resources
<i>Environment</i>	Home facilities and safety
	Potential use of ambulatory pathways/non-acute beds/telehealth
	Transport facilities

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Falls and collapse

A good history, including collateral history from those around the patient, is key to understanding the cause for a fall. Falls are not a normal part of ageing and often point to an underlying pathology or pathologies. Recurrent falls can cause a lack of confidence, ↑ risk of injury, loss of independence, and often institutionalization. A comprehensive geriatric assessment can tease out the multifactorial issues.

Initial assessment of a patient who has fallen

Full history (including collateral history—try to gain this yourself, if possible):

- Circumstance of the fall, e.g. standing (orthostatic hypotension), eating (postprandial syncope), on the toilet (micturition syncope), on turning the head (carotid sinus syndrome), environment (heat, low furniture, loose carpets), witnesses (was there seizure activity? When? Did they lose consciousness?). Note that first-person and collateral descriptions of consciousness are notoriously difficult to interpret.
- Injuries from the fall, e.g. head injuries, musculoskeletal injuries. Axial injuries or absence of defence injuries may suggest loss of consciousness.
- Symptoms experienced around the fall, e.g. pre-syncope (arrhythmias, vasovagal syncope), change in level of consciousness (syncope, seizures), shortness of breath (PE, MI, arrhythmia), palpitations (arrhythmia), fever and signs of infection (sepsis), speech disturbance/limb weakness (stroke, intracranial pathology).
- Previous history of falls and frequency over last year.
- Comorbidities, e.g. IHD, arrhythmias, stroke, Parkinson's disease, cognitive impairment, visual and auditory impairment, mood disturbances.
- Medication review, e.g. antihypertensives, hypoglycaemic agents, sedatives and hypnotics, antiarrhythmics; is there any possibility of OD?
- Functional assessment, e.g. use of walking aids, ability to perform activities of daily living. Visual aids and footwear.
- Nutritional assessment, e.g. unintentional weight loss (malignancy). What do they eat? Who does the cooking? Dehydration?

Examination

The history may guide your examination to focus on a particular system, but bear in mind that most falls are multifactorial, and physicians often concentrate on the 'interesting' causes more than the likely ones. A brief examination of the following systems will highlight any comorbid issues.

Cardiovascular

Lying/standing BP, tachy- or bradyarrhythmias, murmurs (particularly that of aortic stenosis), carotid bruits, ruptured AAA.

Neurological

Gait assessment, peripheral neuropathies, stroke, intracranial bleeds, cerebellar pathologies, visual and auditory impairment, Parkinson's disease, encephalopathy.

Muskuloskeletal

Osteoarthritis or rheumatological conditions causing deformities, muscle wasting, and weight loss, joint stiffness. Pressure sores. Assessing functional ability is important.

Investigations

- Blood tests, e.g. FBC (anaemia), U&Es (renal disease, dehydration), LFTs, glucose (hypo-/hyperglycaemia), vitamin B₁₂ (peripheral neuropathy, nutritional), folate, ferritin, Ca²⁺ (malignancy, arrhythmia, weakness), vitamin D, TFTs (arrhythmia, myxoedema, anaemia), can all be useful.
- ECG (AV block, arrhythmia, MI, prolonged QTc).
- The following should be guided by history/examination:
 - Echo (if signs of valvular heart disease or CCF).
 - 24h ECG monitor—not routine, only if suspicion of paroxysmal arrhythmia.
 - Tilt table testing.
 - Investigations for infection/sepsis—CXR, urine dip, blood cultures, lactate, CRP.
 - CT head if focal neurological signs (malignancy, stroke, SAH, subdural haematoma, normal pressure hydrocephalus) or head injury on anticoagulants.
 - CXR if any signs of hypoxia (underlying chronic lung disease, PE, pneumothorax).
 - Toxicology (paracetamol and salicylate levels, ECG, urine toxicology) if OD suspected.

Management

Treat any underlying cause found, and consider referral to specialist falls services.

Medication review

Polypharmacy increases the risk of side effects such as reduced awareness/reactions, postural hypotension, hypoglycaemia, and ECG abnormalities.

Multidisciplinary team approach

Elderly care physician, physiotherapist, occupational therapist, dietician, psychiatrist (dementia, depression), speech and language therapists, social services.

Refer to a specialist, as indicated by above (cardiology, neurology, oncology, audiology, ophthalmology). Consider ongoing rehabilitation with the multidisciplinary team.

Fragility fractures

A fall from standing height or less resulting in a fracture is defined as a fragility fracture. Hip fractures account for three-quarters of fragility fractures in the elderly, and there is a delay in diagnosis in up to 10% (undisplaced fractures, patient unable to give a history). The mortality and morbidity with a hip fracture is high (up to 13% at 30 days), and these patients should be admitted under an orthopaedic team and operated on within 48h. It is important to always consider a hip fracture in a frail patient, particularly following a fall. These patients should ideally be reviewed by an orthogeriatric specialist prior to theatre.

Non-hip fragility fractures are often encountered on medical units, e.g. vertebral crush fractures, pubic ramus fractures, and wrist fractures. Often there is an underlying osteoporotic process, and surgical techniques can be ineffective. Specialist orthopaedic opinion is key, and in the absence of a surgical option, the following should be considered:

- *Analgesia*: effective pain relief can avoid complications associated with immobility. Regular paracetamol and low-dose opiates can be effective. Consider topical analgesic patches and non-pharmacological approaches [heat patches, transcutaneous electrical nerve stimulation (TENS)]. Prolonged NSAID use is to be avoided.
- *Non-surgical options*: immobilization with plaster/orthopaedic aids helps with analgesia and effective healing.
- *Secondary prevention*: Ca^{2+} and vitamin D replacement should be offered to those who are deficient.
- Bisphosphonates should be prescribed for patients:
 - 75 years or over without the need for a dual-energy X-ray absorptiometry (DXA) scan.
 - 65–74 years if osteoporosis is confirmed by DXA (T-score -2.5).
 - <65 years if: T-score -3.0 standard deviation (SD) or below, or T-score -2.5 SD plus one or more additional age-independent risk factors.
- Alternatives to oral bisphosphonates are available.
- Consider referral to specialist osteoporosis services.
- Underlying causes: assessment of falls risk, as described under  Falls and collapse, pp. 896–7. Smoking cessation and safe alcohol consumption advice. Review medications—long-term steroids, in particular.
- Rehabilitation: early mobilization reduces risks of immobility (VTE, pressure ulcers). Ongoing support from physiotherapists and occupational therapists. May need inpatient rehabilitation at a specialist facility, otherwise consider early supported discharge home with active rehabilitation.

Acute confusion syndrome

Delirium is defined as an acute decline in cognitive function. It is a common presentation affecting 20–50% of patients over 65 in hospital. Distinguishing delirium from a dementia process in the acute setting can be challenging (see Table 17.2). The picture is often complicated by a background history of cognitive impairment. Is this presentation an acute delirium or a progression of dementia, or is there an element of both? Development of delirium in the older patient is a complex interaction between vulnerability of the brain to insult and the degree of the insult. Collaborative history with the next of kin is important to assess the patient’s baseline function and cognition and the timescale of their cognitive decline.

Common causes of delirium

- **Drugs:**
 - Polypharmacy, sedatives and hypnotics (including withdrawal), dopaminergic and anticholinergic medications.
 - Alcohol withdrawal should be considered.
- **Physiological stressors:**
 - Sepsis and infection, dehydration, hypoxia, hypoglycaemia, alcohol withdrawal, constipation, urinary retention.
- **Psychological stressors:**
 - Pain, change of environment.

Table 17.2 Delirium versus dementia

Delirium	Dementia
Acute or subacute	Chronic or subacute
Tends to fluctuate throughout the day	Little fluctuation. ‘Sundowning’ may be evident—cognitive decline seen in the evening
Conscious level usually affected (↓ in hypoactive delirium)	No effect on conscious level
Attention poor and variable	Normal in early stages, progressively worse in later stages
Agitation common (hyperactive delirium)	Agitation not a feature of early dementia, progressively worse in later stages
Hallucinations and delusions not unusual	Not seen in early disease. May be present later. (Lewy body dementia is an exception to this where hallucinations are an early feature. In contrast to delirium, these hallucinations tend to not bother the patient.)
Memory usually severely affected (short and long term)	Short-term memory declines as the disease progresses. Long-term memory usually intact until late stages

Investigations

History (including collateral history)

- *Assessment of cognitive history:* timescale of decline, temporal fluctuation of confusion, previous diagnosis of dementia.
- *Assessment for risk factors:* drug history and recent drug changes, alcohol use, features of infection (lower urinary tract symptoms, cough, vomiting, fever).
- *Co-morbidities:* e.g. DM, Parkinson's disease, depression, psychiatric diagnoses, chronic lung disease, epilepsy.

Examination

A full general examination should be performed, with particular focus on signs of infection, dehydration, focal neurological signs (including meningism), abdominal pain, and constipation.

A measurement of cognitive function, such as the Abbreviated Mental Test (AMTS)⁴ should be performed at this stage to provide a baseline for clinicians assessing the patient's cognition at a later date.

Further tools, such as the confusion assessment method (CAM)⁵ or 4AT, can help distinguish between delirium and dementia, and can be used after a formal assessment of attention and cognition has been performed. These tests should be used by those trained in their use but can identify key features of delirium and dementia.

Focused investigation

- FBC (raised WCC), U&Es (dehydration, AKI), glucose (hypo-/hyperglycaemia), Ca^{2+} (hypercalcaemia and dehydration), CRP (inflammation), TFTs (myxoedema), LFTs (hepatic encephalopathy), drug levels (e.g. valproate, phenytoin), vitamin B₁₂.
- ABG (if hypoxia/hypercapnia suspected).
- CXR (hypoxia, concerns about malignancy—symptomatic hyponatraemia in small cell lung carcinoma).
- ECG (electrolyte disturbances).
- CT head if neurological signs present (stroke, encephalitis, subdural haematoma, SOL).
- LP if encephalitis or meningitis suspected (but do not delay antibiotics).
- EEG (non-convulsive status epilepticus).⁶

Management strategies

- Treat any acute medical issues identified.
- Medication review: address polypharmacy; reduce or stop any psychoactive medication (or note any missing medications, e.g. 'PRN' sleeping tablet actually taken every night).
- Improve sensory impairment: address visual and auditory deficiencies to improve orientation.
- Ensure the patient's safety: avoid bed rails, restraints, 'boxing gloves', and sedation (which will add to the confusion and increase the falls risk).⁷ Use de-escalation techniques, and provide one-to-one nursing care if the patient is at risk of falling or hurting themselves. Discuss with nursing and therapy staff about strategies to maintain calmness—this may include walking with the patient around the ward (if safe to mobilize), rather than trying to continually try to sit them down.

- Provide a low-stimulation environment, if possible: a quiet, private room with good lighting, a window, and a clock for improved orientation. Ensure regular interaction. Provide a daily routine, and encourage family/friends to visit.
- Consider alcohol or nicotine withdrawal. Dependence can be ascertained during a collateral history.

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4. Inouye SK, van Dyke CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;**113**:941–8.
5. Hodkinson HM. Evaluation of a mental test score for assessment of mental impairment in the elderly. *Age Ageing* 1972;**1**:233–8.
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Palliative care and advance care planning

Ideally, the discussion between a physician and a patient about their wishes at the end of life should not occur *in extremis*, but sometimes this is unavoidable. Often older patients with frailty are admitted to hospital acutely unwell and at risk of cardiopulmonary arrest. In this instance, decisions about escalation to invasive treatments and CPR need to be made. Age alone should not be used as a reason for withholding treatment. Approaching the discussion can seem daunting, particularly with patients who feel well at the time.

Determining those patients that might not survive, despite best medical efforts, is extremely difficult. Many physicians recognize that frail elderly patients can make a remarkable recovery from a seemingly hopeless condition. However, it is not unreasonable to consider that, if full, appropriate, and active treatment fails, then even a 'successful' resuscitation is unlikely to leave a frail patient in a better state to benefit from it than before. It is important to be open and honest with the patient (if they have capacity) and next of kin throughout. The following tips can apply to all discussions about resuscitation.

Tips to help the discussion around escalation in the patient with poor prognosis

- Make a diagnosis and present medically appropriate treatment options to the patient/next of kin, highlighting any invasive or uncomfortable treatments so they can consider them.
- Discuss with a senior or colleague if you are unsure of whether further invasive treatment would provide benefit, based on the patient's individual circumstances.
- Be open and honest about the prognosis and likelihood of recovery to the best of your knowledge. The online prognostic calculator, available at  <http://www.epronosis.org>, can help.
- Explain the reasoning behind a 'do not attempt cardiopulmonary resuscitation' (DNACPR) order if placing one, and explain that it does not necessarily mean no treatment will be given.
- Avoid asking the patient if they want CPR when you have decided it would be futile. The decision rests with the multidisciplinary team, not with the patient/next of kin, although it is not appropriate to make such a decision without informing the patient/next of kin or understanding their wishes.
- Offer a second opinion if one is asked for.

Discharging the elderly patient near the end of life

Recognizing when a patient is nearing the end of their life can be very useful for opening the dialogue around future care planning. It offers the patient a chance to think about what they would want and the chance to make advance decisions or appoint a Lasting Power of Attorney to another. Discussion with the patient and/or family before discharge around future wishes can be very helpful for advance care planning. You can provide a realistic picture of the likely progression of a patient's illness and suggest positive treatment goals aimed at improving the quality of life in the last months to year. Polypharmacy can be reviewed at this point, and tablets with no benefit over a year can be stopped, e.g. statins.

Further reading

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Appendix

Reference intervals [908](#)

Guidelines on oral anticoagulation [912](#)

Useful contacts [914](#)

Reference intervals

Biochemistry (always consult your local laboratory)

(See Table A1.)

Table A1	
Substance	Reference interval
ACTH	<80ng/L
ALT	Men <31IU/L
	Women <19IU/L
Albumin	35–50g/L
Aldosterone ¹	100–500pmol/L
ALP	30–300IU/L (adults)
α-fetoprotein	<10kU/L
Amylase	0–180 Somogyi U/dL
Angiotensin II ¹	5–35pmol/L
ADH	0.9–4.6pmol/L
AST	5–35IU/L
Bicarbonate	24–30mmol/L
Bilirubin	3–17micromol/L (0.25–1.5mg/dL)
Calcitonin	<0.1 micrograms/L
Ca ²⁺ (ionized)	1.0–1.25mmol/L
Ca ²⁺ (total)	2.12–2.65mmol/L
Chloride	95–105mmol/L
Total cholesterol	3.9–5.5mmol/L
LDL cholesterol	1.55–4.4mmol/L
HDL cholesterol	0.9–1.93mmol/L
Cortisol (a.m.)	450–700nmol/L
Cortisol (midnight)	80–280nmol/L
CK	Men 25–195IU/L
	Women 25–170IU/L
Creatinine	70 to ≤130micromol/L
CRP	0–10
Ferritin	12–200 micrograms/L
Folate	5–6.3nmol/L (2.1–2.8 micrograms/L)
GGT	Men 11–51IU/L
	Women 7–33IU/L

Table A1 (Contd.)

Substance	Reference interval
Glucose (fasting)	3.5–5.5mmol/L
Glycosylated haemoglobin (HbA1c)	5–8%
GH	<20mU/L
Iron	Men 14–31micromol/L Women 7–33IU/L
LDH	70–250IU/L
Mg ²⁺	0.75–1.05mmol/L
Osmolality	278–305mOsmol/kg
PTH	<0.8–8.5pmol/L
PO ₄ ³⁻ (inorganic)	0.8–1.45mmol/L
K ⁺	3.5–5.0mmol/L
Prolactin	Men <450U/L; women <600U/L
PSA	0–4ng/mL
Protein (total)	60–80g/L
Red cell folate	0.36–1.44micromol/L (160–640 micrograms/L)
Renin (erect/recumbent) ¹	2.8–4.5/1.1–2.7pmol/mL/h
Na ⁺	135–145mmol/L
TSH	0.3–3.8mU/L
Thyroxine (T4)	70–140nmol/L
Thyroxine (free)	10.0–26.0pmol/L
Triglyceride (fasting)	0.55–1.90mmol/L
Tri-iodothyronine (T3)	1.2–3.0nmol/L
Urea	2.5–6.7mmol/L
Urate	Men 0.21–0.48mmol/L Women 0.15–0.39mmol/L
Vitamin B ₁₂	0.13–0.68nmol/L (>150ng/L)

¹ The sample requires special handling—contact the lab.

Urine

(See Table A2.)

Table A2	
Substance	Reference interval
Adrenaline	0.03–0.10micromol/ 24h
Cortisol (free)	≤280nmol/24h
Dopamine	0.65–2.70micromol/ 24h
Hydroxyindole acetic acid (HIAA)	16–73micromol/24h
Hydroxymethylmandelic acid (HMMA, VMA)	16–48micromol/24h
Metanephtrines	0.03–0.69micromol/ mmol creatinine
Noradrenaline	0.12–0.5micromol/24h
Osmolality	350–1000mOsmol/kg
PO ₄ ³⁻ (inorganic)	15–50mmol/24h
K ⁺	14–120mmol/24h
Na ⁺	100–250mmol/24h

Cerebrospinal fluid

See ➡ Lumbar puncture 2, p. 858.

Haematology

(See Table A3.)

Table A3

Measurement	Reference interval
WBC	$3.2\text{--}11.0 \times 10^9/\text{L}$
RBC	Men $4.5\text{--}6.5 \times 10^{12}/\text{L}$ Women $3.9\text{--}5.6 \times 10^{12}/\text{L}$
Hb	Men $13.5\text{--}18.0\text{g/dL}$ Women $11.5\text{--}16.0\text{g/dL}$
Haematocrit (Hct) or packed cell volume (PCV)	Men $0.4\text{--}0.54\text{L/L}$ Women $0.37\text{--}0.47\text{L/L}$
MCV	$82\text{--}98\text{fL}$
Mean cell haemoglobin (MCH)	$26.7\text{--}33.0\text{pg}$
Mean cell haemoglobin concentration (MCHC)	$31.4\text{--}35.0\text{g/dL}$
Platelet count	$120\text{--}400 \times 10^9/\text{L}$
Neutrophils	$40\text{--}75\%$ Abs. no. $1.9\text{--}7.7 \times 10^9/\text{L}$
Monocytes	$3.0\text{--}11.0\%$ Abs. no. $0.1\text{--}0.9 \times 10^9/\text{L}$
Eosinophils	$0.0\text{--}7.0\%$ Abs. no. $0.0\text{--}0.4 \times 10^9/\text{L}$
Basophils	$0.0\text{--}1.0\%$ Abs. no. $0.2\text{--}0.8 \times 10^9/\text{L}$
Lymphocytes	$20\text{--}45\%$ Abs. no. $1.3\text{--}3.5 \times 10^9/\text{L}$
Reticulocyte count ¹	$0.8\text{--}2.0\%$ ($25\text{--}100 \times 10^9/\text{L}$)
ESR	Depends on age (and $\uparrow$ in anaemia) Men (age in years)/2 Women (age in years + 10)/2
PT—factors II, VII, and X	$10\text{--}14\text{s}$
APTT—factors VIII, IX, XI, and XII	$35\text{--}45\text{s}$

¹ Only use percentages if the red cell count is normal; otherwise use absolute values.

Guidelines on oral anticoagulation

(See Table A4.)

For acid–base nomogram on the interpretation of arterial blood gases, see Fig. A1.

For nomogram for body size, see Fig. A2.

Table A4

INR	Clinical condition
2.0–3.0	Treatment of DVT, PE, TIAs; chronic AF
3.0–4.5	Recurrent DVTs and PEs; arterial grafts and arterial disease (including MI); prosthetic cardiac valves

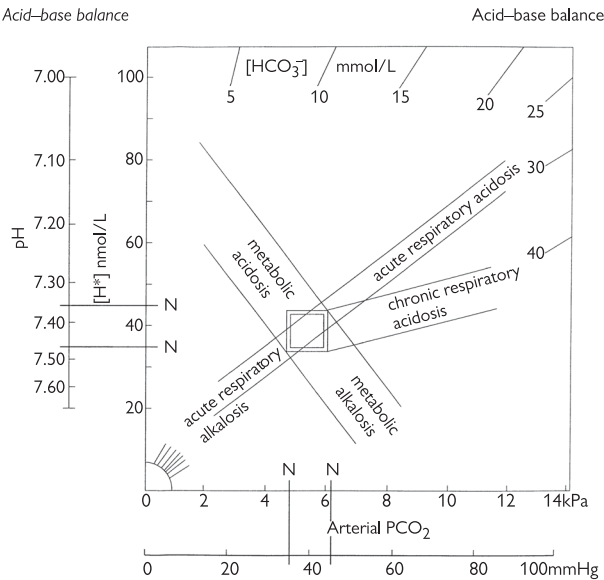


Fig. A1 Acid base nomogram on the interpretation of arterial blood gases.

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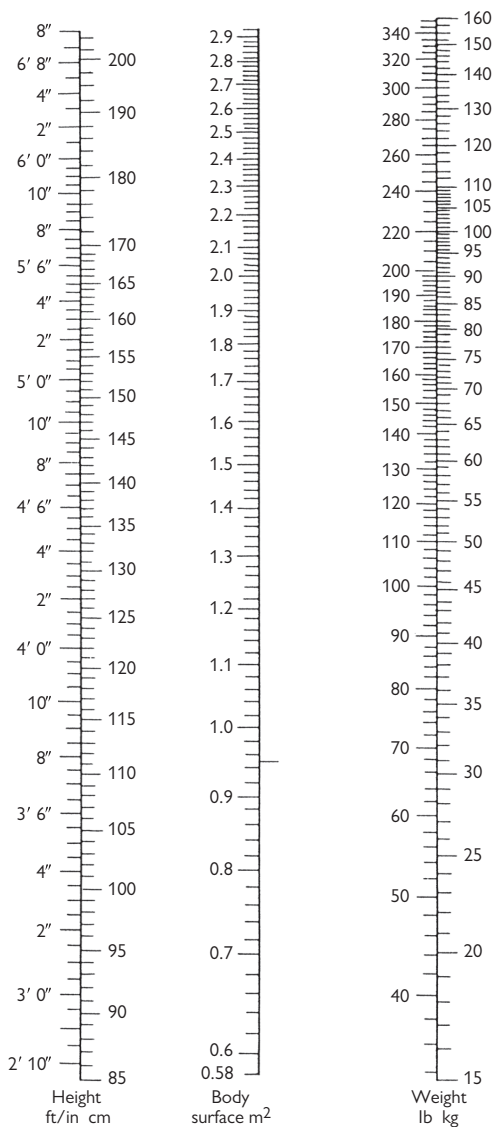


Fig. A2 Nomogram for body size.

Useful contacts

Liver units

Royal Free Hospital, London	0207 794 0500
Addenbrooke's Hospital, Cambridge	01223 245 151
Freeman Hospital, Newcastle	0191 233 6161
Queen Elizabeth Hospital, Birmingham	0121 472 1311
St James Hospital, Leeds 0	113 243 3144
Edinburgh Royal Infirmary, Edinburgh	0131 536 1000
Kings College Hospital, London	0207 737 4000

Organ donation and transplantation

ODT	0117 975 7575
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Poisons units

National Poisons Information Service	0344 892 0111
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Drug and chemical exposure in pregnancy

UK Teratology Information Service	0344 892 0909
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Tropical and infectious diseases

Hospital for Tropical Diseases, London	020 3456 7890: ask for the tropical medicine registrar (or 24h HTD registrar on-call: 07908 250924)
Northwick Park, London	0208 864 3232 (bleep in- fectious diseases registrar)
Liverpool	0151 705 3100 during working hours (out of hours: 0151 706 2000 and ask for the tropical medi- cine physician on-call)

Anti-venom kits for snakebites

For information on identification and management, contact:	
Liverpool	0151 705 3100
London	0207 188 0500

Virus reference laboratory

Colindale, London	0208 200 4400
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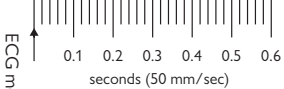
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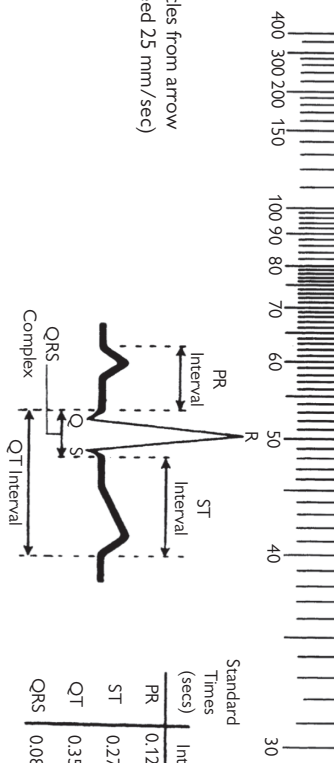
Golden Rules

- 1** The most important person you ever encounter in the hospital is the patient. They are often frightened, and following admission to hospital, they have little say over what happens to them. You need to give some control back to the patient. To do this, they need information from you as to their possible diagnoses and what might happen to them, and they need to be given space to express their views.
- 2** Listening to your patient is the most important thing you can do. Some doctors have this skill, and others do not. If in doubt as to what is wrong with your patient, fall still and just listen to the patient. The diagnosis often becomes obvious if you listen.
- 3** You are the front piece of your hospital. Take pride in where you work, and give your best. If you see someone lost, you should direct them or, better still, show them the way.
- 4** One of the most gratifying aspects of medicine is talking to your patients and their relatives. If you are on call in the evenings, try and take time to talk to the patient and their relatives. Try and avoid situations where you are separated from the patient while talking to relatives, as this can set up distrust where none existed before. Our advice is to be honest, acknowledging doubt when doubt exists, and accept that we can only do what we can do.
- 5** We all have to accept that we will die at some point. With media hype over the years, it has become almost standard practice to try and eke every last ounce of life out of lives that have stopped living. One has to accept that there is a point when it is important to allow a patient to die with dignity. Do not let process and false duty go beyond what is right and dignified for your patient.
- 6** As a junior doctor, you will be frequently asked about results or investigations by the consultant or registrar. If you do not know, it is much better to be honest and just say, rather than make up a result which is wrong. This is obvious, but it is important, since wrong information can lead to harm.
- 7** Many junior doctors agonize over career choices in medicine. There is a place for everyone, and it is important to find the area of medicine that you enjoy and can use and maximize your talents. When making this choice, it is important that you listen to your heart.



ECG measurements

HEART
RATE
Read 2 cycles from arrow
(paper speed 25 mm/sec)



Standard Times (secs)	Interval
PR	0.12-0.22
ST	0.27-0.33
QT	0.35-0.42
QRS	0.08-0.11

